

ANNALS OF INTERNAL MEDICINE

VOLUME 13

JULY, 1939

NUMBER 1

VIRUS INFECTION OF THE CHICK EMBRYO *

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ALTHOUGH physical and chemical methods, especially the former, are being employed extensively at the present time in efforts to elucidate the size, shape, composition and general properties of the ultimate virus particles, an exact determination of their nature as a class has not yet been arrived at; and it is still necessary to resort to the biological method of infecting susceptible hosts, whether cell-suspensions or organized animals and plants, in order to demonstrate and to study the activity of these agents.

Manifestation of a virus activity involves interactions between it and living susceptible cells, in the course of which virus multiplies and the affected cell undergoes a variety of changes, now recognizable as more or less characteristic and individually specific effects of the active agent concerned.

Such demonstrable changes in cells as hyperplasia, development of cellular inclusions, swelling, degeneration, lysis and necrosis in varying proportions and designs constitute the essential representations of the effect of viruses upon the cells susceptible to them; and the one substantial inference to be drawn by students of viruses from the phenomena presented by infected hosts, and from the negative results of attempted culture on dead media, is that living cells are necessary at present for an increase of viruses in quantity. This induction is substantiated whether one hypothecates that viruses are represented by huge proteid molecules elaborated by the infected cell, or that they are minute parasites. In either event one may further infer that multiplication of virus, in the sense of increase in quantity, occurs in the interior of living protoplasm of susceptible cells.

Experimental demonstration of the presence of active virus in the interior of living cells and in relationship with a specific virus inclusion was made several years ago by C. E. Woodruff and myself in our investigations of the pathogenesis of fowl-pox.¹

* Read at the Meeting of the American College of Physicians in New Orleans, March 28, 1939.

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We found that trypsin in weakly alkaline solution would rapidly free the specific cellular inclusions of fowl-pox from infected epithelial cells by dissolving the epithelial membrane and cytoplasm, so that the refractive inclusions, which are relatively quite large and substantial, could be obtained in quantity. By picking out individual inclusions with a micro-pipette and washing them in 2 per cent NaCl solution, until the washings no longer contained demonstrable active virus, we showed that single washed inclusions inoculated into a feather follicle of a hen caused fowl-pox infection at that site. Each well-formed inclusion contains about 50 thousand or more minute particles, uniform in size, coccoid in shape and possessing definite staining reactions. These are incorporated in the inclusions by a lipo-proteid matrix, and they are known as the specific elementary bodies of this disease. By means of an attenuated glass point and a micro-dissector, we were able to break up a single inclusion and to inoculate several feather follicles of a hen with minute fragments containing elementary bodies, and the result was multiple infections with material from one inclusion.²

This evidence indicates very strongly that the elementary bodies of the fowl-pox intracellular inclusion are associated with the specific virus of this disease, and that they become agglomerated within the cell into a cytoplasmic mass, together with a lipoproteid matrix, which is known as the Bollinger body, the specific cellular inclusion of fowl-pox. We have likewise demonstrated that the elementary bodies of *yaccinia* and of *molluscum contagiosum* are intracellular and are the most important constituents of the respective cellular inclusions.

Other evidence that viruses invade and multiply within cells, especially important from the standpoint of pathogenesis, has been derived from experimental infections with viruses which affect nerve cells.

Several years ago Oscar Teague and I obtained experimental evidence that herpes simplex virus gains entrance into the central nervous system of rabbits and spreads there, through the axis cylinders of peripheral nerves, following a peripheral focal infection. These neural processes are of course prolongations of neuronal cytoplasm, and certain neurotropic viruses seem to multiply and to progress within and along these extended cytoplasmic threads from the periphery to the main body of the nerve cell within the ganglia, brain or spinal cord.³ More recently evidence has been obtained by us and by others that a similar axonal transmission of the viruses of rabies, poliomyelitis, equine encephalomyelitis, pseudo-rabies and other neurotropic viruses takes place in experimental infections.

It is thus evident that experimental investigation of virus diseases at the present time requires not only susceptible hosts in which serial transmission can be effected, but also the employment of the technics of cytopathology.

The matter of securing suitable susceptible hosts for the study of virus infections is a problem of the very greatest importance and it involves many special considerations, because it is now well known that viruses may behave differently not only in different hosts, but in different tissues of the same

host. As a result of varying the tissue environment a virus may become suddenly or gradually profoundly modified. For example my colleague, G. J. Buddingh, has recently shown that one passage of fowl-pox virus through the brain of a newly hatched chick will cause a strain of this virus, normally restricted almost exclusively in its effects to squamous epithelium, to become highly infectious for cells of the meninges, of the choroid plexus and of cells of mesodermal origin, namely, endothelium and fibroblasts. This change in the virus appears to be a permanent one and manifests itself even when the usual epithelial tissues are inoculated.⁴

Variation by passage through an alien host is illustrated by modification of a strain of the virus of yellow fever, maintained in monkeys, by passage through the brains of mice, first accomplished by M. Theiler, and this change in the virus has resulted in the acquisition of a vaccine useful for human prophylaxis.^{5, 6, 7}

There are some disadvantages, however, in using various free living animals as hosts for viruses, because animals so used have been found at times to harbor their own viruses which may contaminate that employed experimentally.

For such and other reasons investigators of virus diseases have felt a need for a host, easy of access, in which virus infections generally, might be induced without contamination by bacteria and other viruses. A host that meets many of the requirements has been found in the chick embryo of developing eggs.

In 1931 A. M. Woodruff and I, in searching for a method by means of which we could obtain fowl-pox in quantity free from bacterial contamination, found that the chorio-allantois of developing eggs is a tissue very susceptible to this virus, and the infections resulting from inoculation with fowl-pox reproduced the characteristic lesions and afforded virus in great abundance free from all contamination by other infectious agents.⁸ Buddingh, Woodruff and I later demonstrated that vaccinia and herpes simplex viruses could likewise be cultivated in this tissue in pure strain, notwithstanding the fact that newly hatched chicks are entirely insusceptible to herpes virus and only slightly susceptible to vaccinia.⁹ It thus appeared that we had at hand not only a host usually free of complicating infectious agents, but one highly susceptible to a variety of viruses.

Following these reports the embryonic tissues of the developing egg were used by a number of investigators for the purpose of cultivating and studying viruses,¹¹ and I should like to summarize briefly some of the results that have been obtained.

1. THE SUSCEPTIBILITY OF THE CHICK EMBRYO TO VIRUSES

The cells of the chick embryo have been found to be susceptible to infection by a much greater number of viruses than any other single host. Consequently the embryo may be used as a convenient living medium for the cultivation and experimental investigation of a great variety of these agents.

The following viruses that are pathogenic for man have already been cultivated in this medium, namely, those of small-pox, alastrim and vaccinia; herpes simplex, and virus B., yellow fever and Rift Valley fever; St. Louis encephalitis, lymphocytic choriomeningitis, equine encephalomyelitis, loup-ing-ill of sheep and rabies¹⁰; the common cold, epidemic influenza and psittacosis.

Of viruses affecting animals but to which man is apparently insusceptible, the following have been cultivated in chick embryos: Rous sarcoma, fowl-pox, fowl-plague, infectious laryngo-tracheitis of fowls, New Castle disease, infectious bronchitis of chickens, Pacheco's parrot disease, vesicular stomatitis of horses, myxomatosis of rabbits, ectromelia of mice, sheep-pox and pseudo-rabies.

Thus far among viruses affecting man the following have resisted cultivation in the chick embryo, namely those of molluscum contagiosum, warts, mumps, herpes zoster, varicella, poliomyelitis and measles.

It has been reported that the virus of measles, for which there is no other adequately proved susceptible host than man, has been cultivated in the chick embryo, but there is as yet no acceptable confirmation. Our own efforts in this direction have thus far resulted in failure. However, with improved technics of inoculation now at our disposal, it seems possible that some of the viruses that have resisted cultivation many prove upon further and more intensive investigation to be infectious for this host. Especially should attempts to infect the embryo with the viruses of poliomyelitis and measles be continued and intensified, for successful results might be of great significance for prophylaxis.

2. THE CHICK EMBRYO METHOD AS A MEANS FOR PURIFYING, SEPARATING AND IDENTIFYING VIRUSES

It has been of especial interest to us to observe that the tissues of the chick embryo, including the chorio-allantois, are rather resistant to infection by saprophytes and some common bacterial pathogens, so that it is frequently possible to obtain on primary culture in the membranes a bacteria-free strain of virus originally moderately contaminated. G. J. Buddingh, for example, has obtained bacteria-free strains of vaccine virus from primary inoculation of the chorio-allantois with calf lymph, and with material from a vaccine pustule on a child's arm. Last year he cultured a bacteria-free strain of smallpox virus by inoculating a series of membranes with pus removed directly from cutaneous lesions of a case of variola in the thirteenth day of illness.¹¹

Galloway and Elford have shown that the viruses of vesicular stomatitis and foot and mouth disease could be readily differentiated and separated from mixed infections by a combination of filtration and growth on the egg membrane.¹²

As to the identification of viruses by the chick embryo technic it is to be said that each virus induces more or less characteristic lesions in its

natural host, and when successfully inoculated into the tissues of the chick embryo the same sorts of cellular changes are reproduced. Burnet furthermore has laid great stress upon the chick embryo technic as a means of titrating virus suspensions following dilution and after incubation with specific immune serum.

3. THE CULTURE OF VIRUSES FOR VACCINES

G. J. Buddingh and I in recent years have developed a satisfactory method for preparing antismallpox vaccine in quantity, and free of bacteria, by infecting the chorio-allantois of chick embryos. Modifications of this method have been used by others for the same purpose and with satisfactory results. Our own experience has led us to believe that a vaccine thus prepared could with advantage supplant calf lymph for human antismallpox prophylaxis.¹² A recent extensive report by Stevenson and Butler from the National Lymph Establishment is very favorable to its use. By the use of a modified technic, involving injection of virus into the amnion, Buddingh has recently been able to increase the yield of vaccine many fold, so that the tissues of a single embryo would afford a thousand or more standard doses of vaccine.* The method which he has described of preserving such a vaccine in sterile serum not possible with contaminated calf lymph, greatly prolongs its activity even against the adverse effects of body temperature.

Assuming a rôle of immense importance in individual and mass protection against yellow fever, endemic on two continents, are the recently developed methods of vaccination by the use of attenuated strains of yellow fever virus. The strain used by the International Health Division of the Rockefeller Foundation, with which over a million persons have been vaccinated in South America, is propagated routinely in tissue cultures, but for vaccine production it is inoculated into chick embryos. The infected embryos yield an abundance of virus. The vaccine induces a mild infection, without significant clinical symptoms, and is followed by the appearance of antiviral antibodies in the circulating blood signifying protective immunity.

Among the newcomers of viruses discovered to be pathogenic for man is that of equine encephalo-myelitis, now thought to be an endemic infection among a variety of birds rather than a natural disease of horses. There are two immunologically distinct strains of this virus in our country, namely, the Eastern and the Western strains, and during the past year fatal infection with each has occurred in human beings. Both are highly infectious for chick embryos.

J. Beard has described a vaccine prepared from virus cultivated in the chick embryo and treated with formalin, which is being widely used with apparent success in animal prophylaxis.¹⁴ It is to be hoped that human infection with this virus will not reach proportions requiring similar immunizing procedures.

* Personal communication.

F. R. Beaudette informs me that the New Jersey College of Agriculture supervises the production of laryngotracheitis vaccine at the Vineland Poultry Laboratories to insure purity and potency of the product. This virus is grown on the chorio-allantois with excellent results. That laboratory also produces its pigeon and fowl-pox vaccine in the same way, by cultivation in the chick embryos.

4. INFECTION OF CHICK EMBRYOS AS A MEANS OF INDUCING MUTATIONS AND MODIFICATIONS OF VIRUSES

From the standpoint of practical application of prophylactic vaccination against virus diseases it is of great importance to have a means of reducing the virulence of a particular virus so that a mild or inapparent infection might be induced that would leave the host with a protective immunity. This principle is an ancient one of proved worth in Jennerian prophylaxis against smallpox.

With some viruses it is quite possible to reduce the virulence for a susceptible host by repeated membrane to membrane passage in the developing egg. For example Katherine Anderson, in my laboratory, has recently shown that an increase of virulence for the embryos is acquired by a neurotropic strain of herpes simplex virus during repeated egg to egg passage and this increased virulence is associated with a great loss of pathogenicity for the rabbit. After the thirtieth membranal passage the virus causes extensive hepatic and other internal lesions in the embryo, which are not observed with earlier passages, but the strain at this stage had completely lost its ability to cause encephalitis in the rabbit following corneal infection, and the keratitis following corneal inoculation was so mild as to be almost imperceptible. Such a mild infection, however, calls forth substantial immunity of the cornea.¹⁵

Very promising for an eventual successful vaccine for human epidemic influenza are the results which Burnet and his collaborators have obtained from infection of the chick embryonic membranes with the virus of human influenza.¹² On repeated passage of the "Melbourne" strain of this virus through chick membranes Burnet observed, after the tenth passage, a gradual increase in virulence for this tissue. About the fiftieth passage death of embryos on the third or fourth day began to occur. A rather sudden increase in pathogenicity was observed around the sixty-third passage, all embryos after that stage dying on the third day after inoculation, with striking lesions of hemorrhagic encephalitis. A still further increase of virulence was evident by the seventy-fifth passage, when embryos died within 48 hours and showed multiple hemorrhages in the skin and muscles as well as in the brain.

Corresponding to the gradual development of virulence for the embryo there was a steady loss of virulence for the ferret, and experiments with

human beings indicated that the egg passage virus was almost or completely non-pathogenic when administered intranasally, but was capable of causing a rise in antibody titre in about 50 per cent of those tested. These experiments are quite recent and much more work must be done. To have at hand a means of attenuating the virulence of influenza virus for man is however, a very hopeful beginning.

Increase in virulence for the chick embryo by repeated passage, associated with a reduction in virulence for the native host but with a retention of immunizing power is illustrated also by the virus of infectious bronchitis of fowls. In a recent letter F. R. Beaudette, of the New Jersey Agricultural Experiment Station, has written me that a strain of the virus of fowl bronchitis which he has been cultivating in incubating eggs for some time "seems to have lost its ability to induce disease in fowls entirely, but the killing time for embryos has grown shorter until now it kills in from 24 to 48 hours. Moreover, inoculated chickens seem to develop an immunity to subsequent inoculation with virulent field virus. Similarly fowls tested before inoculation show no neutralizing bodies but they are demonstrable two weeks after inoculation although the chickens have shown no symptoms indicative of infection."

Not all viruses propagated in the embryo exhibit such a great loss of virulence for the usual susceptible host. A strain of vaccine virus, for example, which has been propagated in my laboratory through 250 generations in the membranes during the last seven years by G. J. Buddingh has varied little in its potency for the rabbit and man since the first ten generations several years ago, and is now almost as virulent for rabbit and human skin as the original dermovaccine from which it was derived.

5. THE CULTURE OF VIRUSES FOR CHEMICAL AND PHYSICAL STUDIES OF THEIR NATURE

Lush and Burnet had good results from the use of infected chick membranes as a source of antigens for complement fixation reactions with the viruses of human influenza, swine influenza and rabbit myxomatosis. These were the only viruses tested. Myers and Chapman report that membranes infected with vaccinia provide satisfactory antigens for complement fixation tests.¹²

Our own observations show that infected embryos afford a bountiful source of relatively pure virus in such infections as fowl-pox and vaccinia. The experiments of Katherine Anderson and those of J. R. Dawson, Jr., also indicate that similarly large quantities of the viruses of herpes simplex and of rabies respectively can be obtained from the infected tissues of chick embryos for chemical and physical studies, and possibly as a source of vaccines.

6. ISO- AND HETERO-GRAFTING ON THE MEMBRANES OF CHICK EMBRYOS AS AN INDIRECT MEANS OF STUDYING VIRUS INFECTIONS

As has been already stated there are some viruses which thus far have resisted attempts to cultivate them in the tissues of the chick embryo. In consideration of this failure and because of a desire to study certain problems of immunity experiments were undertaken in order to determine whether or not it would be possible to graft alien tissues onto the chorio-allantoic membrane of chick embryos after the method of Murphy.¹⁸ In this way it might be possible to study virus infection in the tissues of their native host and thus by indirection to create experimental conditions favorable also for studies of cellular and tissue immunity.

Last year Beverly Douglas, Katherine Anderson and I succeeded in grafting human skin upon the chorio-allantois of chick-embryos.¹⁵

We found that the thin skin (Thiersch grafts) adhered and were nourished for as long as 10 days, which represents the longest period available on a single developing egg with the graft implanted at 10 days of incubation. Occasionally regrafts upon a second egg succeeded, thus prolonging the vitality of the graft for several days longer.

In successful experiments the epithelium of the chorio-allantois fuses with that of the graft, the collagen fibers of the chorion interlace with those of the membrane after the separation or disappearance of the ectodermal layer, and the blood vessels of the chick anastomose, or unite by intervening pools of extravasated blood, with those of the graft. This vascular communication between the two tissues is largely responsible for the nourishment of the graft by affording a plasmatic circulation. Gradually there is a revascularization of the graft by an ingrowth of blood vessels from the chick membrane. Isografts and other heterografts, namely rabbit skin, have been successfully grafted in this way.

From the standpoint of studies of infection and immunity to viruses several possibilities for useful application of this method of skin grafting are apparent.

In the first place there is afforded an opportunity to investigate the susceptibility of skin thus grafted to viruses with which so far successful infections of the chick embryo have not been demonstrated, for example, the viruses of measles, chicken-pox, herpes zoster, molluscum contagiosum and warts. If this should prove to be possible, a means would be at hand to study these viruses by indirection and possibly to adapt them to the chick embryo tissues. We have already found that human skin grafts are susceptible to infection with the viruses of smallpox, vaccinia and herpes simplex, but up to the present time we have not had adequate opportunity to study other viruses.

The method is adaptable also to studies of immunity, for the skin of immunized animals can be grafted quite as readily as that of susceptible animals of the same species.

As will be mentioned later we have already made some progress in this direction, although our investigations are still incomplete.

7. USE OF THE CHICK EMBRYO FOR STUDYING IMMUNITY

There are many problems of immunity that need new technical approaches and our experiments with chick embryos early indicated that they might advantageously be used in certain ways to investigate some phases of the immunity phenomena.

From the standpoint of natural immunity our early experiments with the virus of herpes simplex demonstrated that tissues of the chick embryo are highly susceptible to infection by this agent notwithstanding the fact that newly hatched chicks seem to be completely resistant. Here is a problem of the utmost significance—the acquiring of complete resistance from a state of high susceptibility by the processes of maturation—and an experimental animal available for its investigation. We have begun preliminary study of this phenomenon, but our progress thus far has not been sufficiently extensive to report at this time.

It is a matter of common knowledge that hosts which recover from an infection by most viruses become resistant to subsequent infection by the same virus for varying periods of time, not infrequently for life. This is an example of acquired immunity—a result of the phenomena of infection. Under such circumstances it is usually possible to demonstrate that the host has acquired certain properties differing from those present during the previously susceptible state. One of these properties is the capacity of the blood serum to prevent virus from causing infection in an otherwise susceptible host. Following certain infections whether viral or bacterial the serum possesses also the capacity to agglutinate and to dissolve the infective agent. The dissolving effect seems to be dependent upon complement, usually present in normal serum, acting in conjunction with a specific antibody.

So far as our experiments have gone it appears that the chick embryo does not possess the capacity to produce specific antibodies, in effective amount if at all, and our investigation concerning the presence of complement has shown that none can be demonstrated up to the time of hatching.

These facts present an interesting situation with reference to analyzing certain factors of immunity, because it has long been known that under certain circumstances a temporary immunity can be conferred upon a susceptible host by introducing into its body the serum or blood of a host that has recovered from the disease against which protection is desired.

We have since developed a method whereby antisera, with or without complement, can be injected directly into the blood stream of chick embryos, so that analyses can be made of the various factors concerned in the processes involved in passive immunization.

With respect to the immunity that follows a virus infection there is the very important question as to whether all the phenomena of immunity are due to change in the body fluids, i.e. humoral immunity, or that the cells of the immune host themselves possess an acquired resistance. This question is an especially pressing one in relation to virus immunity because it is now quite generally accepted that a virus must penetrate certain cells of the host in order to multiply and thus induce disease.

Katherine Anderson and I have recently undertaken a study of some of these questions in relation to immunity to fowl-pox, using especially the method of grafting skin from normal and immune chickens onto the chorio-allantoic membrane of chick embryos.

Following recovery from fowl-pox chickens become completely immune to subsequent inoculation with the virus of this disease. The tissue specifically affected by this virus is the epithelium of the skin, consequently this tissue offers an exceptionally favorable opportunity for the grafting experiment.

Skin from normal and from immune chickens was grafted together or alone upon the chorio-allantois of developing eggs after 10 or 12 days of incubation. After four days, at which time they were well established, the grafts were inoculated with fowl-pox virus. The result was that the epithelial cells from immune chickens became infected quite as readily as those from normal chickens.

In other words we have as yet found no evidence to support the view that epithelial cells acquire an intrinsic immunity as a result of fowl-pox infection. These experiments are being continued in an effort to discover the mechanism of acquired resistance, but we cannot make a more extensive report at the present time.

SUMMARY

The success of future studies of infections caused by viruses, and the state of immunity that frequently follows, will depend very largely upon the experimental animal used. Likewise, so far as one can foresee, we must rely upon suitable hosts, whether they be living cells in tissue cultures or organized living animals and plants, for obtaining antigenic substances and vaccines to be used in attempts to improve methods of prophylaxis.

Although efforts to employ the chick embryo for these purposes are recent and the results limited, enough has already been accomplished to indicate that this method holds much promise of usefulness, and it is my opinion, based upon our own experiences during the past few years, that if it should be given a more general application to such problems as I have indicated, its use would facilitate progress in virus research.

REFERENCES

1. WOODRUFF, C. E., and GOODPASTURE, E. W.: The infectivity of isolated inclusion bodies of fowl-pox, *Am. Jr. Path.*, 1929, v, 1.
2. WOODRUFF, C. E., and GOODPASTURE, E. W.: The relation of the virus of fowl-pox to the specific cellular inclusions of the disease, *Am. Jr. Path.*, 1930, vi, 713.
3. GOODPASTURE, E. W.: Herpetic infection, with especial reference to involvement of the nervous system, *Medicine*, 1929, viii, 223.
4. BUDDINGH, G. J.: A meningo-encephalitis in chicks produced by the intracerebral injection of fowl-pox virus, *Jr. Exper. Med.*, 1938, lxvii, 921 and 933.
5. SELLARD, A. W.: Immunization in yellow fever and other virus diseases, *New England Jr. Med.*, 1937, ccxvi, 455.
6. THEILER, M., and SMITH, H. H.: The use of yellow fever virus modified by in vitro cultivation for human immunization, *Jr. Exper. Med.*, 1937, lxv, 787.
7. ELMENDORF, J. E., JR., and SMITH, H. H.: Multiplication of yellow fever virus in the developing chick embryo, *Proc. Soc. Exper. Biol. and Med.*, 1937, xxxvi, 171.
8. WOODRUFF, A. M., and GOODPASTURE, E. W.: The susceptibility of the chorio-allantoic membrane of chick embryos to infection with the fowl-pox virus, *Am. Jr. Path.*, 1931, vii, 209.
9. GOODPASTURE, E. W., WOODRUFF, A. M., and BUDDINGH, G. J.: The cultivation of vaccine and other viruses in the chorio-allantoic membrane of chick embryos, *Science*, 1931, lxxiv, 371.
10. BURNET, F. M.: The growth of viruses on the chorio-allantois of the chick embryo. *Handbuch d. Virusforschung*, R. Doerr and C. Hallauer, 1938, Julius Springer, Wien. First Half, p. 419.
11. DAWSON, J. R., JR.: Infection of chicks and chick embryos with rabies, *Science*, 1939, lxxxix, 300.
12. BUDDINGH, G. J.: Infection of the chorio-allantois of the chick embryo as a diagnostic test for variola, *Am. Jr. Hyg.*, 1938, xxviii, 130-137.
13. BUDDINGH, G. J.: Production and use of smallpox vaccine virus cultivated in the chorio-allantoic membrane of chick embryos, *Am. Jr. Pub. Health*, 1937, xxvii, 1135.
14. STEVENSON, W. D. H., and BUTLER, G. G.: Studies on the cultivation of vaccinia on the chorio-allantoic membranes of chick embryos. Report on Public Health and Medical Subjects. No. 87. Ministry of Health, London, 1939.
15. BEARD, J. W., FINKELSTEIN, H., SEALY, W. C., and WYCKOFF, R. W. G.: Immunization against equine encephalomyelitis with chick embryo vaccine, *Science*, 1938, lxxxvii, 490.
16. ANDERSON, KATHERINE (unpublished work).
17. GOODPASTURE, E. W., DOUGLAS, BEVERLY, and ANDERSON, KATHERINE: A study of human skin grafts upon the chorio-allantois of chick embryos, *Jr. Exper. Med.*, 1938, lxxviii, 89.
18. MURPHY, J. B.: Studies in tissue specificity, *Jr. Exper. Med.*, 1914, xix, 181.

VISUALIZATION OF THE CHAMBERS OF THE HEART AND THE THORACIC BLOOD VESSELS IN PULMONARY HEART DISEASE; A CASE STUDY *

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PULMONARY heart disease, or *cor pulmonale*, has long been known as a disorder which tends to develop in the course of certain chronic pulmonary diseases. Emphysema^{1, 2, 3} and pulmonary fibrosis^{4, 5, 6} have, perhaps, been mentioned most frequently in this connection, but other types of lung disease which cause extensive obliteration or narrowing of the smaller pulmonary blood vessels may produce it.⁷ Among these are primary endarteritis obliterans of the pulmonary arteries^{8, 9}; obliterative endarteritis due to metastatic carcinoma^{10, 11} and *Schistosomiasis mansoni*¹²; chronic pulmonary embolism^{13, 14}; and the pulmonary fibrosis and emphysema produced by spinal and thoracic deformity.^{15, 16, 17} The principal pathological changes occurring in the heart consist of dilatation and hypertrophy of the right ventricle,^{18, 19} particularly the outflow tract^{20, 21} although in advanced cases the inflow tract also is involved, dilatation of the pulmonary artery and its larger divisions and, eventually, with the onset of heart failure, enlargement of the right atrium. The left ventricular hypertrophy so frequently associated with this condition is probably due to systemic hypertension or other independent causes of heart disease,³ although myocardial anoxemia has been cited as an etiological factor.² It is generally agreed,^{3, 19, 22} although not unanimously,² that the enlargement of the right ventricle and the pulmonary artery is caused by the pulmonary hypertension which develops as a result of the increased resistance to blood flow through the pulmonary circulation in chronic lung disease.

Although the pathological changes in pulmonary heart disease are well defined, the diagnosis of this disorder presents unusual difficulty, for there are no pathognomonic symptoms or physical signs. The dyspnea, cough, cyanosis, and weakness so frequently encountered and ascribed to early cardiac failure are due entirely to the underlying pulmonary disease.¹⁹ Enlargement of the right ventricle cannot be detected accurately by percussion, and the systolic murmur frequently heard at the pulmonic area and the accentuation of the pulmonic second sound are not distinctive. Right axis deviation of the electrocardiogram is not a constant or dependable

* Presented at the Twenty-Third Annual Meeting of the American College of Physicians, New Orleans, La., March 28, 1939.

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This investigation was aided by a grant from the Department of Medical Research of the Winthrop Chemical Company, Incorporated.

guide³ in this disease. Measurement of the circulation time has no diagnostic value,²³ and the venous pressure remains normal²⁴ except in the presence of right ventricular failure, although an elevation of the venous pressure in uncomplicated emphysema has been reported.¹ There is evidence that the saline infusion test of myocardial efficiency may permit the recognition of this disorder²⁴ but experience is yet too limited to warrant any conclusion. In the absence of heart failure, *cor pulmonale* is symptomless and unobtrusive; and, when heart failure does supervene, the evidence must be looked for in the engorgement of the peripheral veins, enlargement of the liver, ascites, and dependent edema, and not in disturbance of the pulmonary circulation. Since other clinical methods have consistently failed in the detection of this type of heart disease, it has been necessary to employ roentgenology for its diagnosis.

The value of roentgenologic examination of the heart has been appreciated almost since Roentgen's discovery of the x-ray in 1895. Since then the characteristic appearance of the cardiac silhouette in the various types of heart disease has been worked out and is now generally known. Dietlen²⁵ was probably the first to investigate the heart in emphysema. He reported his orthodiagraphic studies in this condition as well as in mitral and aortic valvular disease in 1908, and described the rounded shape, the apparent smallness and the low central position of the heart in the chest which he ascribed to the low diaphragm. Groedel²⁶ in 1912 commented upon the clear visibility of the apex of the heart and the inferior vena cava in this condition and questioned whether the apparent smallness of the heart was due to an actual decrease in size or to its central position and elongation. Both these observers recognized that independent heart disease frequently modified the cardiac outline in emphysema. Three years later, Staehlin²⁷ confirmed these observations and called attention to the poor definition of the aortic arch and to the prominence of the middle curve of the left border of the heart in the frontal view which appeared to be pulled up. In 1916, Lutembacher²⁸ described the striking prominence of the pulmonary arc in five patients with great enlargement of the right ventricle. In his book in 1924, Dietlen²⁹ summarized the roentgenographic evidence of right ventricular hypertrophy in emphysema. He noted enlargement of the heart transversely to the right, protrusion of the lower right edge of the heart which was separated from the right auricle above by a notch, prominence of the pulmonary arc with forceful pulsation there and at the lower right cardiac border, and lengthening of the right ventricular curve in side view. Vaquez and Bordet³⁰ described the bulb-shaped heart due to transverse cardiac enlargement and the prominence of the larger pulmonary vessels. They also observed the "sabot" heart in emphysema. Assman³¹ emphasized the enlargement of the pulmonary curve and the prominence and pulsation of the hilar blood vessels. Finally Clerc and Mourrut³² reported a case of *cor pulmonale* and completed the roentgenographic picture of this condition by emphasizing the enlargement of the hilar blood vessels and their

tortuous descending branches on each side which they likened to a "moustache."

In their comprehensive study of the heart in emphysema, Parkinson and Hoyle³ reviewed the literature on this subject and reported in detail their clinical and roentgenographic observations in 80 patients with high grade emphysema, 58 per cent of whom had pulmonary heart disease. They noted the frequency with which the heart was affected by other cardiovascular disease, notably hypertension, although it frequently escaped the involvement due to emphysema. They observed roentgenographic changes in the stem and the branches of the pulmonary artery in 58 per cent of their series. These consisted of enlargement and increased density of the right and left branches of the pulmonary artery and their branches in the hilar and surrounding area. Undue prominence of the pulmonary arc was observed in 35 patients (44 per cent) but not the excessive pulsation or the striking degree of enlargement characteristic of mitral stenosis and congenital heart disease. These changes in the main pulmonary artery and the primary branches could generally be demonstrated more clearly in the oblique positions. Enlargement of the "pulmonary conus," they believed, was the most frequent indication of actual cardiac enlargement in emphysema, although it was detectable less often than the pulmonary arterial changes. It was rarely demonstrable in the frontal view, requiring the right oblique projection for its detection. Involvement of the body of the right ventricle offered unusual difficulty in recognition, for it could rarely be shown in the frontal view, and only in a small proportion of cases in the left oblique position which is the projection of choice. Enlargement of the right atrium was noted infrequently, and that of the left atrium only once—in a patient with auricular fibrillation. Left ventricular enlargement usually due to hypertension was present in 30 per cent of their cases.

These authors tried to apply the conventional methods of cardiac measurement to the diagnosis of pulmonary heart disease but concluded that mere inspection of the heart shadow by an experienced observer was more reliable than any system of measurement. Measurements of the transverse diameter, the cardio-thoracic ratio, and the transverse diameter in the left oblique position by Fray's method, were unsatisfactory as indices of cardiac enlargement because of the barrel shape of the chest and the long narrow form of the heart. Measurements of the pulmonary conus and artery by the methods of Vaquez and Bordet and Abreu likewise were found to be unreliable guides to enlargement of these structures. Commenting upon the unsatisfactory results obtained with cardiac measurement in this disease, Parkinson and Hoyle stated: "There would be advantages in a reliable scheme for measuring enlargement of individual chambers of the heart and of the great vessels. But we are convinced that this is not yet feasible except when such enlargement is of a very gross kind." Accurate measurement of the chambers of the heart, the pulmonary circulation and the great

vessels has, however, become a possibility since the publication of their paper in January, 1937.

We have recently developed a practical method for visualizing the heart and the thoracic blood vessels.^{33, 34} It consists of the rapid intravenous injection of a concentrated (70 per cent) solution of diodrast into a large vein of the arm and the taking of roentgenograms at the moment of opacification of the structures to be visualized. In normal individuals the superior vena cava and the right atrium are filled in one to one and a half seconds after the beginning of injection, the right ventricle and the pulmonary artery and its branches in three seconds, and the left atrium, the left ventricle and the aorta in from six to ten seconds. In the right heart, the following structures have been identified: The superior vena cava and its tributaries; the right atrial and ventricular cavities and walls; the auricula; the tricuspid valve; the trabeculae; the ventricular septum; the pulmonic valve, and the pulmonary artery with its sinuses and subdivisions. The following components of the left heart have been seen and studied: The pulmonary veins; the left atrial and ventricular walls and cavities; the auricula; the cusps of the aortic valve, and the entire thoracic aorta including the sinuses and the innominate, the left common carotid, and the left subclavian branches from the arch.^{34, 35} Characteristic changes in heart³⁶ and lung disease^{37, 38} have been reported.

The purpose of this paper is to demonstrate the value of detailed visualization of the heart and the thoracic vessels in a patient with pulmonary heart disease and to indicate its importance in the recognition of this not uncommon but frequently overlooked condition.

CASE REPORT

H. G., an unemployed, 57 year old, white American laborer was admitted on March 23, 1938, because of an attack of "faintness" which had occurred three hours earlier. Because of uncoöperation and defective memory, an adequate history was unobtainable. For many years he had had cough and the expectoration of yellow mucoid sputum which, in his estimation, amounted to six to eight ounces daily. He denied having had hemoptysis or chest pain, but had experienced moderate dyspnea upon climbing two flights of stairs. For the past three years he had been unemployed and homeless and had eaten irregularly, having had only soups and stews with an occasional sandwich. He admitted the excessive use of alcohol in the past with an average ingestion of a quart of whisky a day until the past year when it, too, had become difficult to obtain. He had always considered himself well and denied any previous illnesses; although he finally recalled that many years ago he went to a chest clinic because he thought he might have pulmonary tuberculosis. Apparently he was reassured, for he had no further occasion to seek medical care. The attack of "faintness," which was the first he had ever experienced, occurred on the street, and a passerby summoned an ambulance. On arrival at the hospital, the patient denied convulsive seizures, precordial pain, and any symptom except the "faintness" and the cough and expectoration.

Examination on entry showed the patient to be poorly developed and nourished, and he appeared to be chronically ill. His temperature was 102 degrees. He was slightly dyspneic while lying flat in bed but not orthopneic, for the dyspnea was not

relieved by elevation of the bed. Both pupils were irregular and reacted sluggishly to light. Ophthalmoscopic examination revealed only a moderate degree of tortuosity of the vessels and no hemorrhages or exudates. The tongue and mouth were essentially normal, but examination of the throat was not possible because the patient refused it. The thorax was barrel shaped with flaring of the costal margins, and the

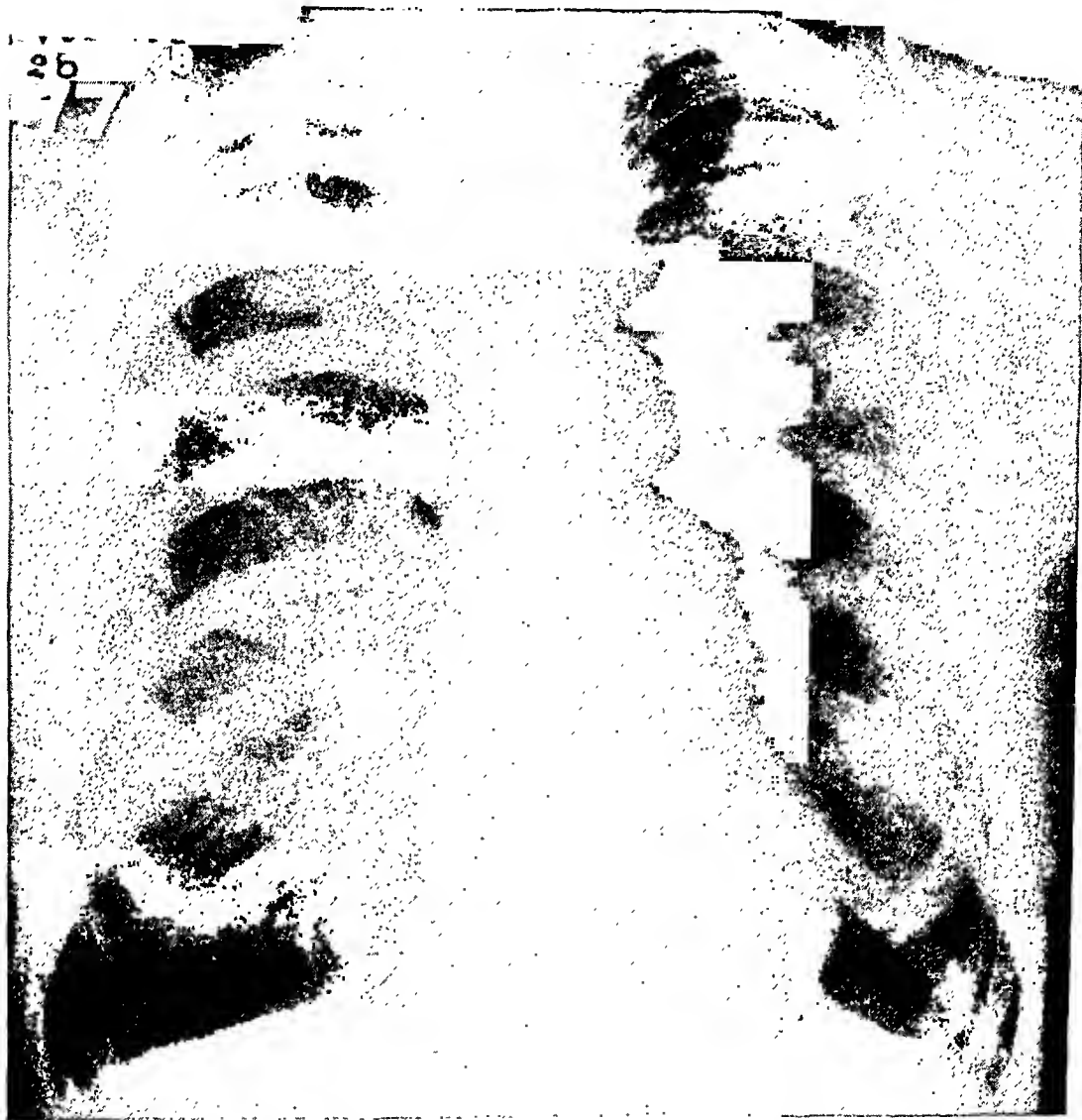


FIG. 1. *Conventional Roentgenogram—Frontal View.*

Note central position of heart, prominence of right lower border and pulmonary arc and calcification of aortic knob. Hilar blood vessels and right inferior branches unusually prominent. Decreased vascularity of mid and peripheral zones, widened interspaces, and large emphysematous bulla at right base characteristic of emphysema. Note cavity with fluid level in lung near right hilum.

chest moved *en masse*. There was hyperresonance to percussion and the breath sounds were diminished throughout. Expiration was prolonged with expiratory wheezing. The point of maximum impulse of the heart was in the fifth interspace, 8.5 cm. from the midsternal line and within the midclavicular line. The heart sounds were distant; the aortic second sound was moderately accentuated, ringing in character, and greater

than the pulmonic second sound which, however, seemed louder than normal. There was a faint systolic murmur at the aortic area and either a split first sound or soft systolic murmur at the apex. No pulmonic murmur could be heard. The rhythm was regular with a ventricular rate of 100. The blood pressure was systolic, 100, and diastolic, 60. The abdominal examination was entirely negative; the liver was palpable at the costal margin only on deep inspiration; and there was no ascites. Except for a moderate degree of cyanosis of the nail beds and slight to moderate sclerosis of the radial and brachial arteries, the extremities were not remarkable; there was no venous engorgement, edema, or clubbing. Examination of the neuromuscular systems revealed no abnormality except for tenderness of the calf muscles.

Laboratory Examinations: The urine was repeatedly normal. The erythrocyte count varied between 3.09 and 3.9 millions per cu. mm. and the hemoglobin from 10.2 to 11.3 grams per 100 cu. cm. The morphology of the red blood cells was normal. The leukocyte count on admission was 9,050 with the following distribution of cells: polymorphonuclears, 58 per cent, lymphocytes, 36 per cent, and monocytes, 2 per cent. The Wassermann test was negative, and the chemical examination of the blood showed no abnormality; the non-protein nitrogen was 33 and the blood sugar 120 mg. per cent. The sputum examination made on admission was negative for the tubercle bacillus, and the sputum typing performed on the same day showed unclassified pneumococci. The blood culture was sterile. The vital capacity was 1.9 liters, equivalent to 1.09 liters per square meter of body surface, which represented a decrease of 58 per cent below the average normal.

The conventional six-foot roentgenograms to be described later showed localized and generalized emphysema, calcified tubercles in the right upper lung field, and a cavity of unknown etiology in the lower part of the right upper lobe near the hilum. The heart was triangular in shape, enlarged transversely to the right with striking prominence of the pulmonary arc. The aortic knob was prominent and showed a small area of calcification. An attempt to fill the pulmonary cavity with iodized oil was unsuccessful, but the right middle and lower lobe bronchi were outlined and showed the slight dilatation of the terminal bronchioles frequently found in emphysema. Esophagrams taken in the frontal, the lateral, and both oblique positions were entirely normal.

Conventional electrocardiograms showed regular sinus rhythm, no deviation of the electrical axis, and slurring of the QRS in Leads II and III. The T-wave was low in Lead I and diphasic in II and III. Precordial electrocardiograms taken from points V_1 to V_6 were normal except for inversion of the T-wave at V_3 .

Course: On entry the patient appeared acutely as well as chronically ill. His temperature varied between 100 and 102 degrees, reaching a maximum of 103 degrees on the seventh day. Subsequently the fever subsided and his temperature remained normal until his discharge on May 23, 1938, two months after admission. While on the ward his sputum was noted to be mucopurulent, and postural drainage was attempted but was unsuccessful because the patient would not coöperate. On routine hospital diet, the evidence of peripheral neuritis disappeared; and after ten days of hospital care, he felt completely well and became ambulatory. Since discharge he has been seen at frequent intervals in the Outpatient Clinic and no change has been observed in the status of either the heart or the lung disease.

Clinical Diagnoses:

I. General:

Peripheral neuritis due to avitaminosis B_1 .

II. Pulmonary:

Chronic pulmonary tuberculosis, IA, healed. (Right apex.) Chronic bronchitis. Pulmonary fibrosis. Bullous and generalized emphysema. Pulmonary cavity of unknown etiology (lower part of right upper lobe).

III. *Cardiac:*

- (a) (etiologic) Pulmonary fibrosis, emphysema, and arteriosclerosis.
- (b) (pathologic) Right ventricular hypertrophy, dilatation of the pulmonary artery, and dilatation and atherosclerosis of the aorta. Coronary sclerosis (probable).
- (c) (physiologic) Regular sinus rhythm.
- (d) (functional) IIA (slight diminution of cardiac reserve).

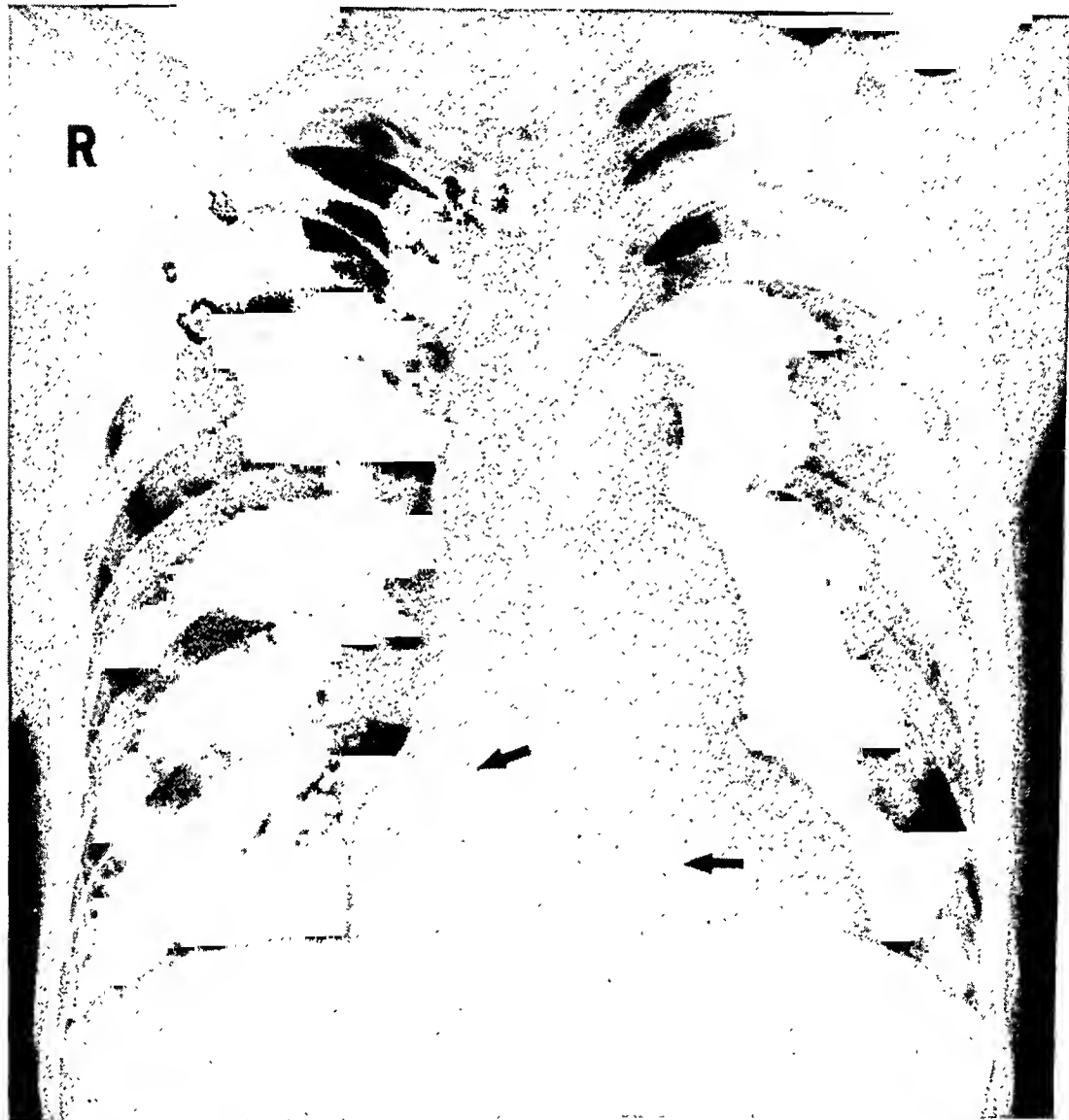


FIG. 2. *Contrast Roentgenogram—Frontal View 4½ seconds after beginning of injection.*

Superior vena cava, left innominate vein and its tributaries opaque. Right atrium, right ventricle, and pulmonary artery well filled. Right atrial and pulmonary arterial walls well defined, 2 mm. in thickness. Lower arrow against ventricular septum, upper arrow indicates junction of superior vena cava and inner border of right atrium.

ROENTGENOLOGIC STUDIES:

1. *Roentgenoscopic Observations.*

The diaphragm was low and its excursion slight. The lung fields were well illuminated especially at the right base where there was a circumscribed bulla. At the

right hilar area there was a small cavity with a fluid level which shifted with change of position and was localized at the right mid lung field. The heart in all views showed normal pulsations, those on the left side being greater than those on the right. The pulmonary artery appeared dilated and the hilar vessels were larger and denser than normal while those to the outer zone were decreased in number and size. There was no "hilar dance" and the aortic pulsations were normal. The optimal angle for the right anterior oblique projection proved to be 35° and that for the left oblique view 40° .

2. Conventional Teleoroentgenograms.

In the frontal view (figure 1), the position of the diaphragm was low and the ribs appeared more horizontal than normal with widened interspaces. The large emphy-

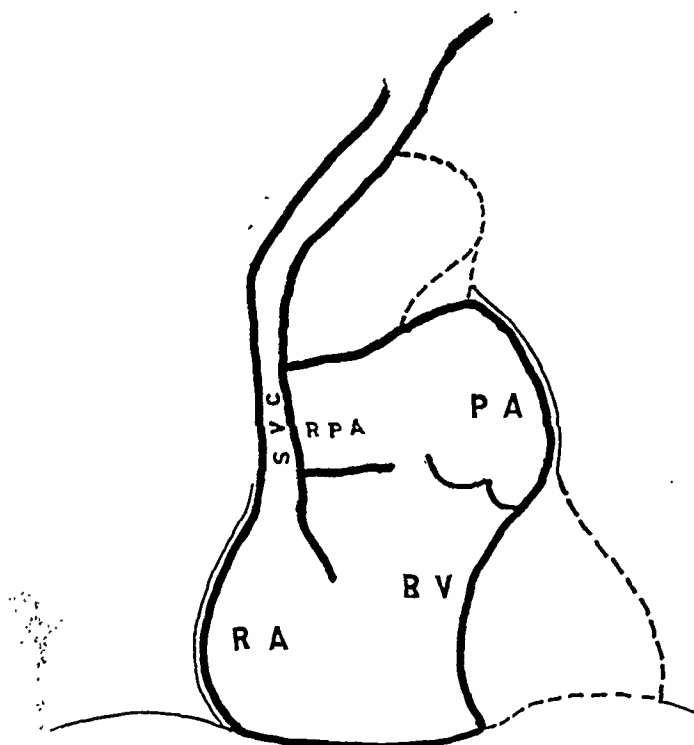


FIG. 2A. Tracing.

S. V. C. = superior vena cava; R. A. = right atrium; R. V. = right ventricle; P. A. = pulmonary artery; R. P. A. = right pulmonary artery. Note right and left cusps of pulmonary valve and atrial and pulmonary arterial walls.

sematous bulla on the oblique and the lateral views (figures 5, 8, 11) appeared to have a fibrous wall. Elsewhere the lung fields showed interstitial fibrosis. The right apex and the first interspace contained a few calcified tubercles (figure 1). Adjacent to the right hilum was a small cavity with a fluid level. On lateral view (figure 11), this was in the mid lung field and, subsequently, by bronchographic examination, was shown to be in the lower part of the upper lobe. The postero-anterior diameter was moderately increased.

The heart on frontal view (figure 1) was roughly triangular in shape and appeared to be more centrally placed than normally. The lowest curve of the right cardiac border was unusually prominent and the pulmonary arc was conspicuously enlarged, appearing as a prominent bulge between the aortic and the left ventricular contours. The left ventricle appeared to be normal but the aortic arch was more

prominent than usual and contained a calcified plaque. The right innominate vein and the superior vena cava were visible lying to the right of the aorta.

The right anterior oblique projection (figure 5, rotation 40°) showed conspicuous enlargement of the pulmonary artery, elongation of the heart and dilatation and

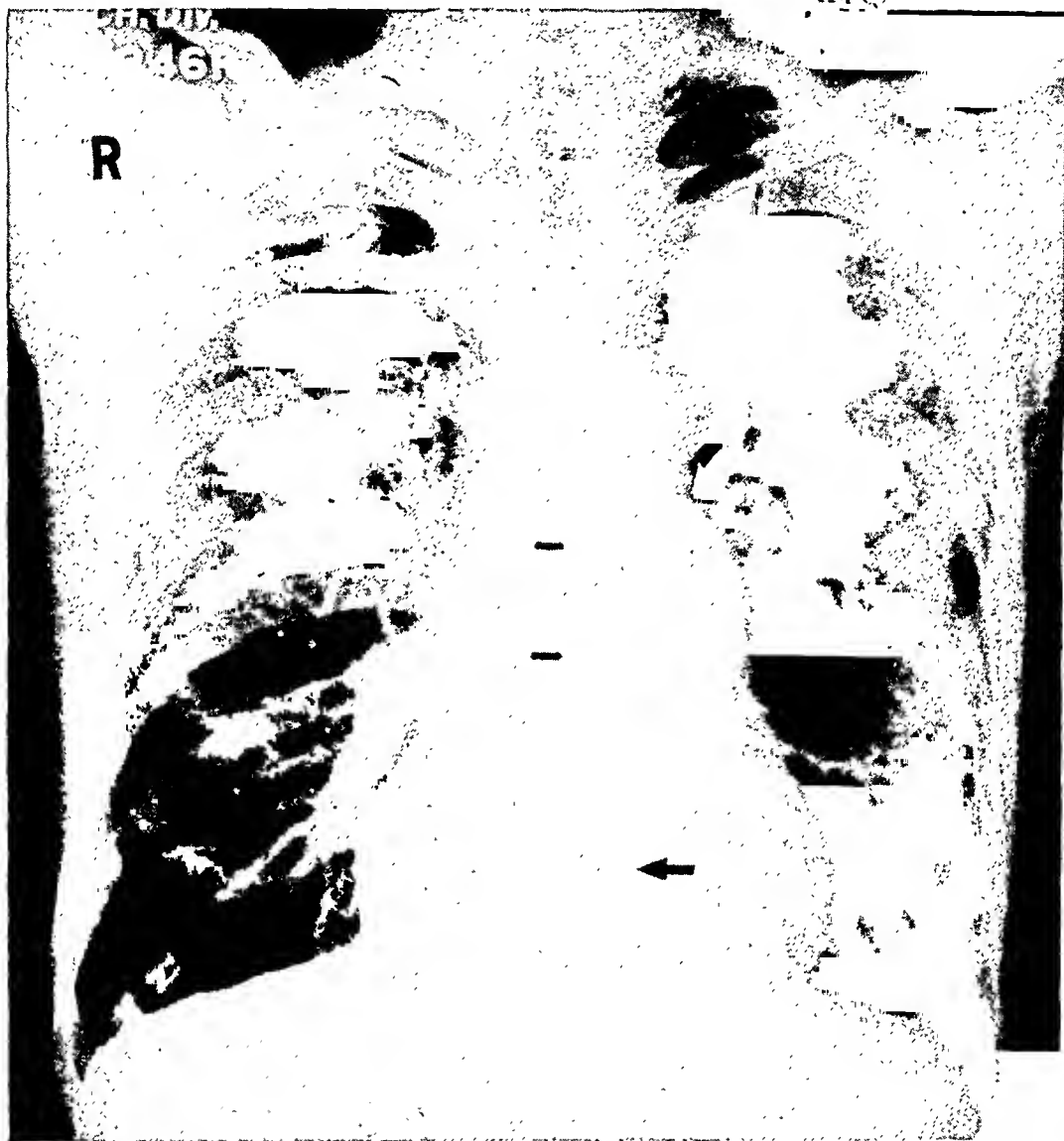


FIG. 3. *Contrast Roentgenogram—Frontal View at 6 seconds.*

Right atrium no longer opaque. Ventricular septum, left border of pulmonary artery, receding left branch and right main trunk clearly defined. Right border of ventricle and conus arteriosus indistinct. Note enlargement of the pulmonary artery and its branches as far as fourth subdivisions and decreased vascularity in mid and outer zones giving the appearance characteristic of emphysema. Black arrow denotes ventricular septum; white arrow arching and receding left pulmonary artery; parallel lines embrace right pulmonary artery.

increased density of the thoracic aorta. The retrocardiac space was clear and the esophagram, as previously noted, was of normal contour.

The left anterior oblique position (figure 8, rotation 40°) showed an unusual prominence of the lower half of the right contour, but there was no angulation of

this side. The left border was normal in shape and cleared the spine at this rotation. The receding right branch of the pulmonary artery, which was seen as the rounded density near the ascending aorta, was distinctly enlarged, as was the left branch which crossed the "aortic window" in lateral view. The aortic outline was indistinct but the arch appeared to be widened; no calcification was visible in this view.

In the lateral position (figure 11) the heart appeared to be enlarged transversely, as were the pulmonary artery and the aorta.

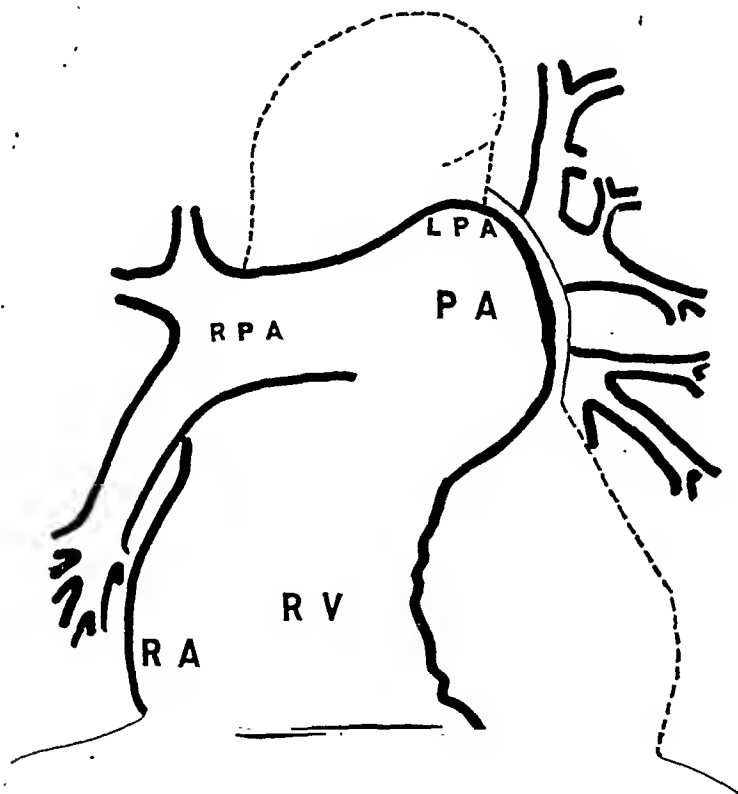


FIG. 3A. Tracing.

R. A. = right atrium; R. V. = right ventricle; P. A. = pulmonary artery; L. P. A. = left pulmonary artery; R. P. A. = right pulmonary artery.

3. Contrast Telorocentgenograms.

I. Frontal View:

FIGURES 2 AND 2A MADE $4\frac{1}{2}$ SECONDS AFTER THE BEGINNING OF INJECTION. The left innominate vein with its tributaries, the subclavian and basilic veins, the superior vena cava, the right atrium, the right ventricle, and the pulmonary artery were opaque. The innominate vein measuring 1.2 cm. in diameter crossed the spine to join the superior vena cava which could be followed to the right atrium. At this point, the superior vena cava measured 1.4 cm. in diameter. The right atrial wall was clearly outlined and was 2 mm. in thickness. The ventricular septum was displaced to the left, lying 9.2 cm. from the right border of the heart. Only the left border of the conus arteriosus and the pulmonary artery were visible, but two cusps of the pulmonary valve were identified. The pulmonary artery formed the prominent pulmonary arc, and its wall measured 2 mm. in thickness.

IN FIGURES 3 AND 3A, TAKEN $1\frac{1}{2}$ SECONDS LATER, the right ventricle, the pulmonary artery and both main branches were visible, but the right atrium was no longer opaque.

The right ventricle formed a vertical band of density 5.5 cm. wide which rested upon the diaphragm below and passed upward and to the left to end as the conus arteriosus. The left branch of the pulmonary artery could be seen only as an upward extension of the pulmonary arterial density noted in the previous film. The right pulmonary



FIG. 4. *Contrast Roentgenogram—Frontal View at 12 seconds.*

Left ventricular cavity, ascending and transverse portions of aorta, innominate, left common carotid, and subclavian arteries well outlined. Large vertical arrow points directly to ventricular septum which curves upwards and to right. Left ventricular cavity lies above and to left of arrow; ventricular wall well defined and inner border indicated by horizontal arrow. Parallel lines enclose ascending aorta. Note thickness of wall at aortic knob. Small arrows upon branches at arch.

arterial branch was outlined distinctly as it crossed to the right and divided at the hilum. Its diameter was 3.4 cm. and that of the descending branch 1.8 cm. at its origin and 1.4 cm. at the level used by Assman.³¹ The pulmonary arterial branches in the inner and middle zones seemed thicker, denser, and stiffer than normal, while there was decreased vascularity towards the periphery.

FIGURES 4 AND 4A, MADE AT 12 SECONDS. The left atrium, the left ventricle, and the ascending and transverse portions of the aortic arch were well filled. The left ventricular cavity appeared to be somewhat enlarged. There were two curved lines along the left border of the heart. The irregular inner one, which was continuous with the left ventricular cavity, appeared to represent the inner border of the ventricular wall. It lay 1.4 cm. from the outside of the heart; whereas the more distinct middle curve in the apical region measured 7 mm. from the outer border. The left aortic cusp and the inner border of the aorta were faintly outlined. The diameter of the ascending aorta measured 3.4 cm. and the aortic wall 3 mm.

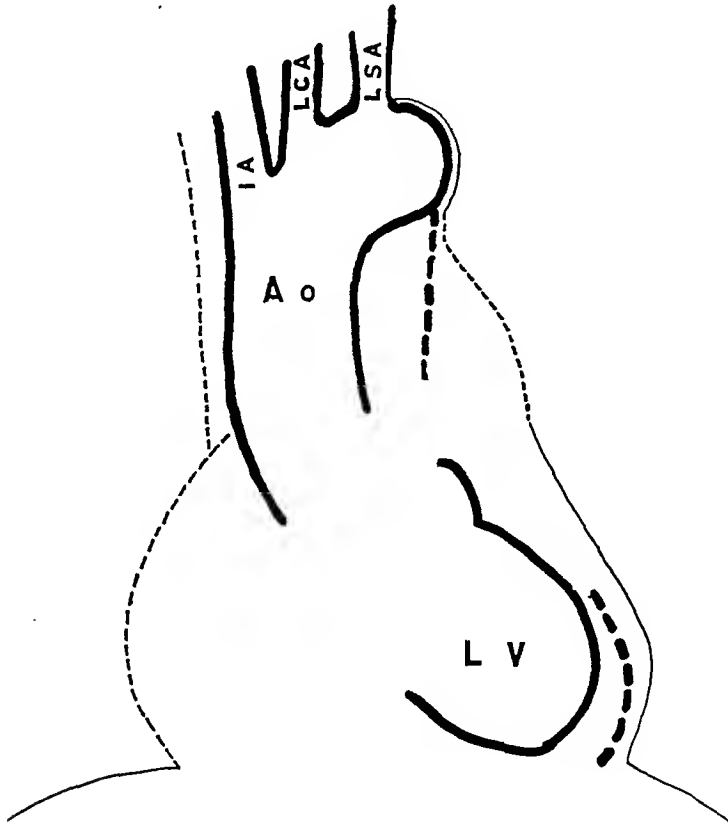


FIG. 4A. Tracing.

L. V. = left ventricle; Ao. = aorta; I. A. = innominate artery; L. C. A. = left common carotid; L. S. A. = left subclavian artery. Note dotted line at apex dividing ventricular wall, also parallel course of innominate vein and artery and that superior vena cava lies well beyond aorta.

.II. Right Anterior Oblique Projection (Rotation 35°):

FIGURES 6 AND 6A, MADE AT 5½ SECONDS. The superior vena cava, the right atrium, the inflow and outflow tracts of the right ventricle, the left posterior cusp of the pulmonary valve, the pulmonary artery and its right and left branches were opacified. The right atrium lay immediately behind and slightly above the right ventricle and measured 5.8 cm. in the vertical diameter and 3.4 cm. in the horizontal. The coronary sulcus indicating the site of the tricuspid valve was clearly seen. The inflow portion of the right ventricle, which extended from the coronary sulcus to the apex of the right ventricle, measured 8.5 cm. in length and 5.5 cm. in depth, while the outflow portion taken from the apex of right ventricle to the pulmonary cusps was 8.7 cm. Trabeculations and narrowing of the cavity anteriorly produced ir-

regularity and the lessened density near the apex. The conus was well outlined and appeared to be widened, having a diameter of 3.8 cm. The pulmonary artery was strikingly enlarged, measuring 4.0 cm. in diameter and 4.5 cm. in length; and the right branch was dilated, having a diameter of 3.2 cm. at the bifurcation of the main trunk. Its subdivisions also were enlarged, the inferior trunk being 1.9 cm. in diameter at its origin.

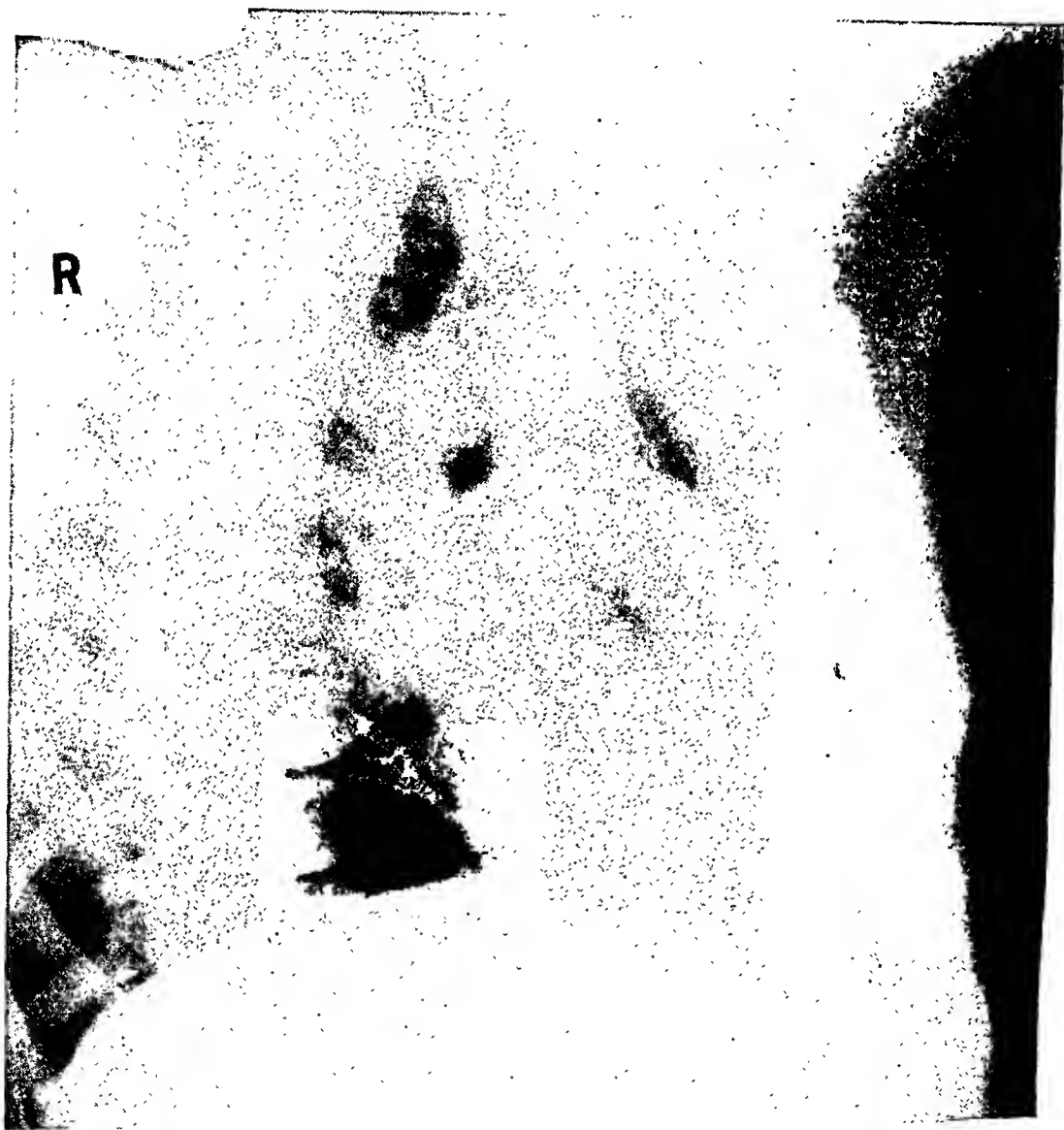


FIG. 5. *Conventional Roentgenogram—Right Anterior Oblique Projection.*
Note increased horizontal diameter of heart and angular prominence of pulmonary curve.
The aorta is larger and denser than normal.

FIGURES 7 AND 7A, MADE AT 11 SECONDS. The left atrium, the coronary sulcus, the left ventricle, the left aortic cusp, the aortic sinuses, and the aorta with its branches from the arch were well visualized. The left atrium measured 5.0 cm. in vertical diameter and 3.0 cm. horizontally. The left ventricle from the coronary sulcus to the apex measured 10.5 cm. The internal diameter of the aorta immediately above the

sinuses was 3.3 cm. and the total diameter 4.1 cm. The aortic wall was well defined and measured 4 mm. in thickness.

III. *Left Anterior Oblique Projection (Rotation 40°):*

FIGURES 9 AND 9A, MADE AT 4.5 SECONDS. The right atrium was outlined although partly obscured by the overlying right ventricle. The inflow tract was seen as an indistinct rounded shadow near the diaphragm extending from the right border to the septum and measuring 6.2 cm. transversely. Its outer wall was 5 mm. in thickness. The outflow tract appeared as a vertical band of density extending from the diaphragm to the pulmonary orifice and measured 7.8 cm. in length and 4 cm. in diameter at the conus. The pulmonic cusps were faintly outlined. As in the right oblique view the pulmonary artery appeared conspicuously dilated having a diameter of 4.5 cm.; its length could not be determined accurately. The diameter of the left branch at the bifurcation was 4.4 cm.

FIGURES 10 AND 10A, MADE AT 11 SECONDS. The left atrium, the left ventricle, and the entire thoracic aorta, including the sinuses and the branches from the arch, were visualized. The left atrium formed a rounded density lying behind the upper left quadrant of the heart into which the superior pulmonary vein emptied. The left ventricle forming the remainder of the left cardiac shadow lay in front of the atrium overlapping its anterior border; at this point there was an elliptical shadow. The ventricular septum formed the convex anterior border of the left ventricular cavity, midway between the right and the left borders of the heart. The thickness of the left ventricular wall could not be estimated. Two cusps of the aortic valve were visible midway between the right and left borders of the heart, and above them the entire thoracic aorta which showed a moderate degree of generalized enlargement and "unfolding." The diameter of the ascending aorta was 4 cm., the transverse aorta 3.5 cm., the descending portion 3.4 cm., and the entire length of this vessel from the aortic valve to the diaphragm was 30.5 cm.

IV. *Left Lateral Projection:*

FIGURES 12 AND 12A, MADE AT 4½ SECONDS. The faintly outlined right innominate vein and superior vena cava passed downward midway between the spine and the sternum to enter the right atrium. The right atrium, the right ventricle with the pulmonic cusps, and the pulmonary artery with its sinuses and both major branches were opaque. The right atrium appeared as a round shadow lying behind the center of the cardiac mass and covered anteriorly by the inflow tract of the right ventricle which extended to the cardiac apex. The anterior border of the heart was formed exclusively by the outflow tract of the right ventricle, whose wall measured 5 mm. in thickness. The posterior border of the outflow tract except at the conus arteriosus was not visualized. As in the other views, the pulmonary artery was strikingly enlarged, measuring 4.1 cm. in diameter immediately above the sinuses and 4.4 cm. in length. With its right and left branches, the pulmonary artery formed the letter Y.

FIGURES 13 AND 13A, AT 11 SECONDS. The left atrium, the left ventricle, and the ventricular wall were faintly but definitely outlined, while the aorta was clearly visualized. The left ventricular wall measured 14 mm. and the diameter of the aorta was the same as that observed in the oblique positions. The left atrium lay posteriorly and superiorly near the spine, and anterior to it was the left ventricle, overlying it in part and separated from it by the oval density observed in figure 10. Two aortic cusps, with the corresponding sinuses, were well defined. As in the left oblique view the aorta appeared moderately dilated and the arch widened.

DISCUSSION

This case study illustrates the value of detailed visualization of the heart and the thoracic blood vessels in the diagnosis of pulmonary heart disease. Visualization in this instance did not contribute to the recognition of the

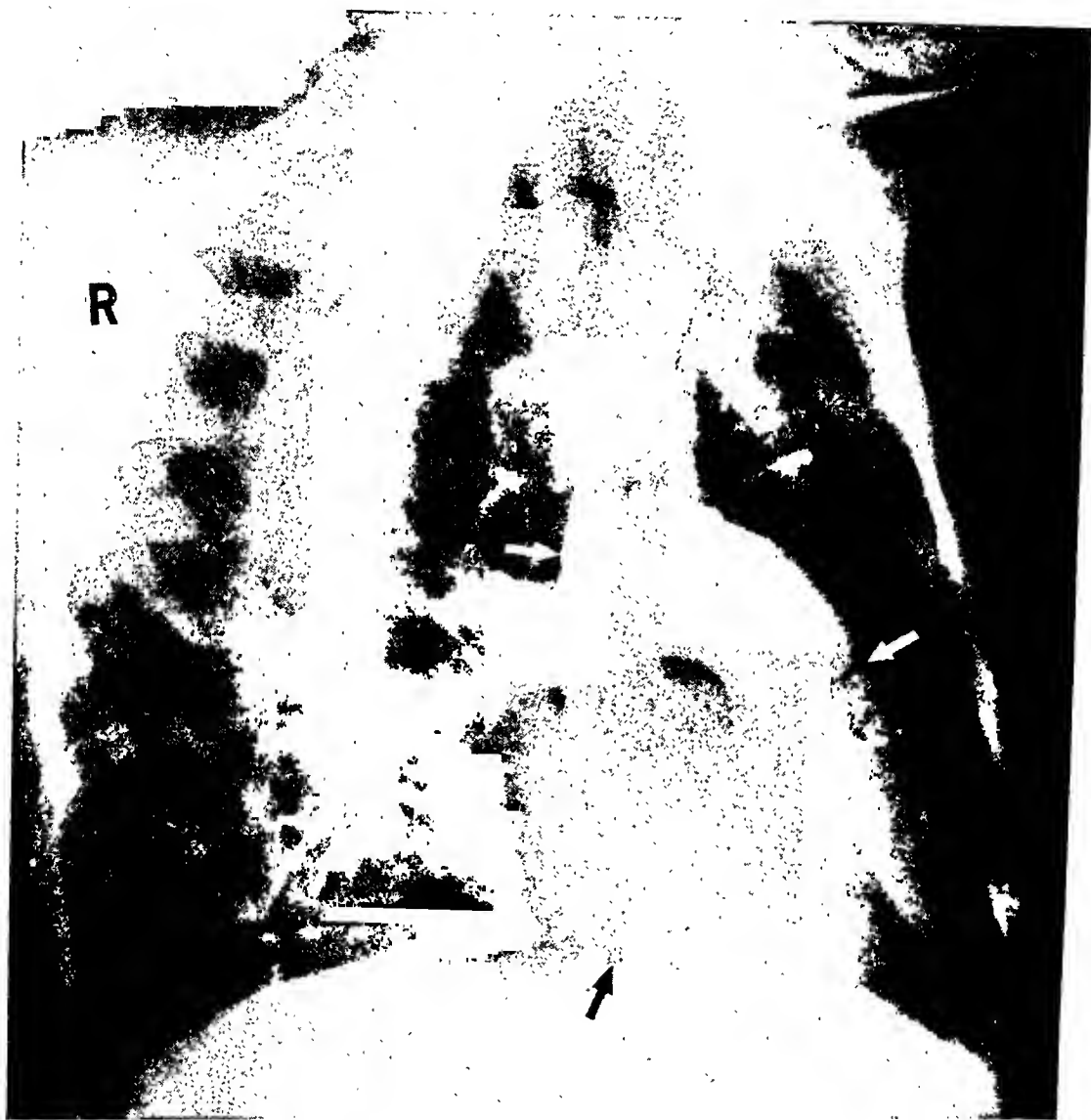


FIG. 6. *Contrast Roentgenogram—Right Anterior Oblique Position at 11 seconds.*

Left atrium, left ventricle, and ascending and transverse aorta outlined. Black arrow points to coronary sulcus; white arrow lies on left ventricular wall and indicates cavity. Small arrow lies in aorta and points downward into left cusp. Note aortic wall thickness on both sides of ascending aorta.

heart disease, which was obvious from the conventional roentgenograms. It did, however, provide a wealth of exact information regarding the structural and the functional state of the chambers of the heart, the great vessels, and the pulmonary circulation, which permitted accurate localization of the disease and appraisal of its degree.

The absence of pathognomonic symptoms and signs in pulmonary heart disease and the importance of roentgenographic examination in its diagnosis are well demonstrated by this study. Although the history of chronic bronchitis and the presence of pulmonary fibrosis and emphysema implied some degree of disease of the pulmonary artery and the right ventricle^{2, 3, 6} physical examination gave no definite evidence of it. The heart was not enlarged to percussion and palpation, and there were no abnormal pulsations or murmurs which could be related to the right ventricle or the pulmonary artery. While there was some accentuation of the second sound at

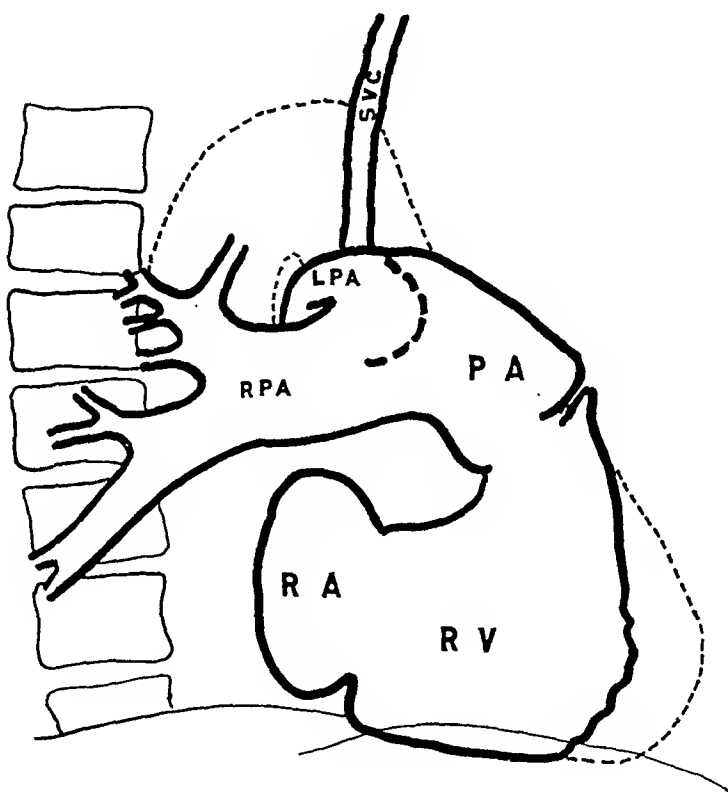


FIG. 6A. *Tracing.*

S. V. C. = superior vena cava; R. A. = right atrium; R. V. = right ventricle; P. A. = pulmonary artery; L. P. A. = left pulmonary artery; R. P. A. = right pulmonary artery.

Note bifurcation of pulmonary artery and upward arching of left branch.

the pulmonic area, it might have been due to transmission from the aortic area as well as to pulmonary hypertension and arteriosclerosis. Even the cyanosis could not rationally be ascribed to right ventricular disease and failure in the absence of venous engorgement, dependent edema, and hepatic enlargement. The vital capacity was strikingly reduced but, like the cyanosis, was undoubtedly a result of the chronic pulmonary disorder and unrelated to either right or left sided heart disease. The electrocardiogram, likewise, gave no assistance in the detection of pulmonary heart disease since there was no deviation to the right of the electrical axis or other evi-

dence of selective involvement of the right ventricle. The circulation times to the lungs and the carotid sinus, which were determined before visualization by our modification of the ether and the cyanide methods,^{33, 34} showed a



FIG. 7. *Contrast Roentgenogram—Right Anterior Oblique Projection at 5.5 seconds.*

Superior vena cava, right atrium, inflow and outflow tracts of right ventricle, pulmonary artery and its right and left main divisions opacified. Black arrow points to coronary sulcus indicating location of tricuspid valve. Inflow tract of right ventricle extends horizontally to apex and outflow tract vertically to pulmonary orifice. Pulmonary valve indicated by white arrow. Decreased density and irregularity of anterior part of ventricle due to narrowing of cavity and trabeculations. Note striking dilatation of pulmonary artery and main branches. Bifurcation indicated by arrow.

moderate slowing of the blood flow from the arm to the pulmonary capillaries but a normal velocity between the lungs and the carotid sinus. Although such delay in the peripheral venous blood flow may occur in emphysema, according to Kountz and his associates,² it cannot be regarded as a

characteristic feature of *cor pulmonale*. Since the foregoing methods of study had failed to establish the diagnosis, it was necessary to employ roentgenology for the recognition of this disorder.

Fluoroscopic and roentgenographic examinations revealed the classical picture of *cor pulmonale* frequently seen in older patients in whom there is also arteriosclerotic or hypertensive heart disease.^{29, 30} In the frontal view, the heart was low, centrally placed, and triangular in shape. This configuration was caused in large part by the rounded prominence of the right lower border which was almost a mirror image of the left contour; and the triangular appearance was enhanced by the striking enlargement of the pul-

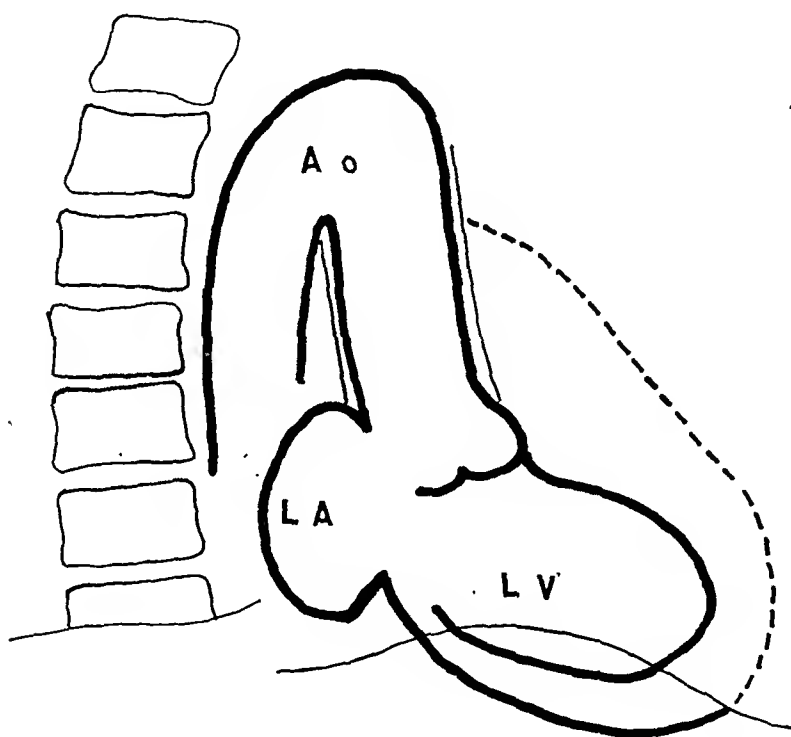


FIG. 7A. Tracing.

L. A. = left atrium; L. V. = left ventricle; Ao. = aorta. Note cusps of aortic valves and thickness of aortic wall.

monary arc which completely obliterated the usual concavity and replaced it by a convex bulge. Contrary to the observations of Dietlen²⁹ the pulsation of the lower right cardiac border and the pulmonary arc was not unusually forceful. The hilar blood vessels and their descending branches were increased in size and density as described by Clerc and Mourrut,³² Parkinson and Hoyle³ and others, but not to the degree frequently seen, and certainly not enough to merit the term "moustache." However, the smaller vessels were typical of pulmonary fibrosis and emphysema in that they were strikingly decreased in size and number and appeared stiff and wire-like in the middle and peripheral zones. Study in the oblique positions completed the

roentgenographic picture of *cor pulmonale*. In the right oblique view the pulmonary arc was strikingly prominent and angular; and the right branch of the pulmonary artery as it crosses the spine and the left receding branch were obviously enlarged. The long axis of the heart also appeared length-



FIG. 8. *Conventional Roentgenogram—Left Anterior Oblique Projection.*

The right lower border of heart unusually prominent. Moderately enlarged aortic arch lies above; below is the conspicuously enlarged pulmonary artery with left branch almost filling "aortic window." Large oval density in pulmonary artery indicates receding right main branch.

ened in this view. In the left oblique position, the characteristic enlargement of the left branch was evident as this vessel crosses the "aortic window" beneath the unfolded aortic arch. These roentgenologic features in the presence of chronic pulmonary disease and the absence of mitral

stenosis, congenital heart disease, goiter, and myxedema heart warrant the diagnosis of pulmonary heart disease.

Although the evidence provided by conventional roentgenology has been invaluable in the diagnosis of this type of heart disease it, nevertheless, is relatively crude and gives but a poor insight into the condition of the heart and the pulmonary vessels. The significance of the changes in the size and the shape of the cardiac silhouette and of the pulmonary vessels has been established broadly by necropsy examination and postmortem visualization study, but interpretation in the individual case is difficult and inexact. It is known that right ventricular enlargement is manifested in the frontal view, first by prominence of the pulmonary arc due in part to upward elongation of this chamber and displacement of the pulmonary artery and, later, by transverse widening of the ventricle causing displacement of the right atrium to the right and of the left ventricle to the left and posteriorly. The boundaries of the right ventricle, however, cannot be determined accurately during life; and it is, therefore, impossible to estimate the degree of enlargement or to tell whether or not this chamber reaches to the right lower border of the heart or enters into the formation of the pulmonic arc. Likewise, the location of the pulmonary artery is indicated by the prominent pulmonary arc which it forms; but the size, the shape, and the course of the stem and the main branches cannot be seen in the frontal view, for they are concealed by the mediastinal and hilar densities.

The oblique views give better definition of the pulmonary artery and its branches, but these structures still are dimly outlined for only a short distance and neither their beginning nor end can be seen distinctly. At best, the anterior border of the main trunk is visible for only a few centimeters in the right oblique view, but its diameter and length cannot be determined and it is soon lost in the supracardiac shadow. Its right branch likewise is poorly defined (figure 5). In the left oblique position, the pulmonary artery cannot be recognized, but, because of the clear space termed the "aortic window" in this view, the left branch can often be seen.^{3,30, 31, 41, 42, 43, 44} In both oblique positions the site of bifurcation of the pulmonary artery may frequently be identified by the rounded shadow which represents the receding main branch seen on end; the other branch crosses the lung field to disappear in the spinal density (figures 5 and 8). Angulation and prominence of the right cardiac border in the left oblique position is a reliable sign of right ventricular enlargement⁴¹; but it is obvious, since the location of the ventricular septum and the thickness of the right ventricular wall cannot be established, that any estimate of the degree of hypertrophy or dilation of this chamber must be very inexact. Similarly in the right oblique view, elongation of the long axis of the heart can be recognized, but it is impossible to know where the right ventricle begins and ends and how much it is enlarged. Since the pulmonary valves and sinuses are invisible, it is impossible to distinguish the pulmonary artery from the conus arteriosus and, therefore, to decide whether or not the conus reaches to the surface of the cardiac sil-

houette and is border forming. These and other important problems may now be solved by detailed visualization.

The advantages of visualization of the interior of the heart over ordinary roentgenologic examination have been illustrated by the contrast roentgeno-



FIG. 9. *Contrast Roentgenogram—Left Anterior Oblique Position at 4.5 seconds.*

Superior vena cava, right atrium, right ventricle, and enlarged pulmonary artery with main divisions filled. Upper black and lower white arrows embrace inflow tract of right ventricle. Lower black arrow points to beginning of outflow tract. Upper white arrow rests upon auricle and against conus arteriosus. Note ventricular wall thickness.

grams. Instead of an undifferentiated shadow of the heart and the larger vessels, visualization provides an accurate plan in which the size, the shape, and the location of each major structure can be seen. By the use of two or more projections, a three dimensional concept of each chamber and vessel may be obtained in which their complex anatomic relationships become dis-

cernible or at least better understood. As we have previously emphasized,³⁴ the frontal and lateral positions are ideal for visualization of the main stem of the pulmonary artery which is seen in end and side views respectively, and for the blood vessels at the hilum and in the lung. But because of the position of the heart within the chest, the oblique positions are essential for adequate study of the architecture of the heart, the right and left branches of the pulmonary artery and the aorta since these positions provide end and

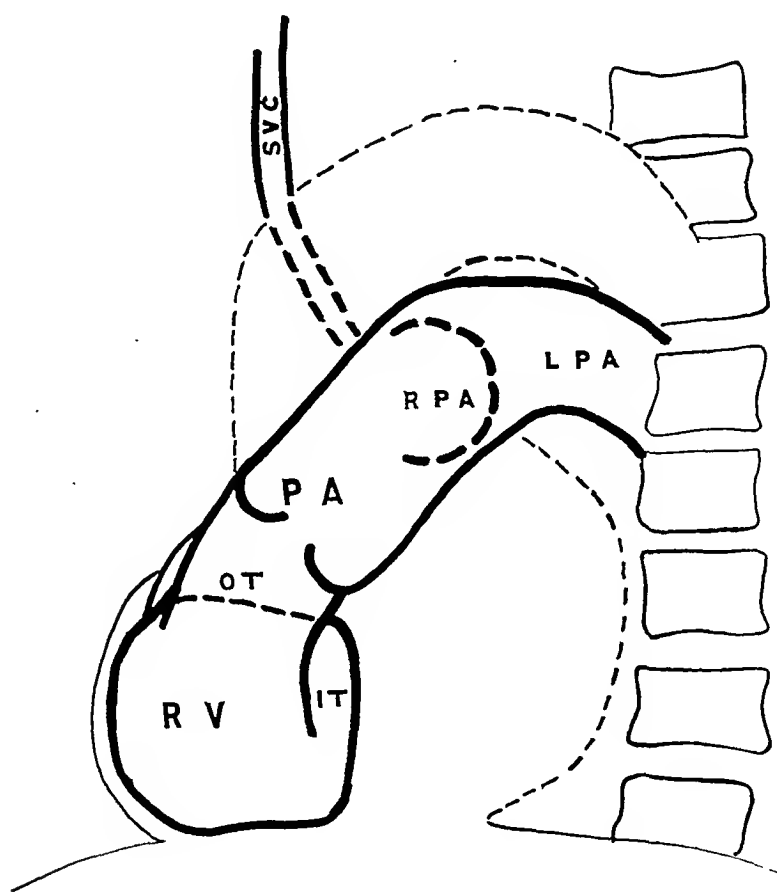


FIG. 9A. *Tracing.*

S. V. C. = superior vena cava; R. V. = right ventricle; I. T. = inflow tract; O. T. = outflow tract; P. A. = pulmonary artery; R. P. A. = right pulmonary artery; L. P. A. = left pulmonary artery.

Note pulmonary cusps.

lateral projections of these structures which are suitable for accurate interpretation and mensuration. Interpretation of the contrast roentgenograms in this case is based upon the evidence provided by Gray's Anatomy,⁴⁵ the anatomic and roentgenographic studies of Kirch,^{20, 21} Vaquez and Bordet,³⁰ Nemet,⁴¹ Nemet and Schwedel,⁴² Assman,³¹ Laubry and his associates,⁴⁰ Brenner,³⁹ Schwedel and Epstein,⁴³ Parkinson and Hoyle,³ Rubin⁴⁴ and others, and upon our own postmortem study of other hearts. Direct confirmation by necropsy has not been possible since the patient is still alive.

The following detailed information regarding the heart, the great vessels and the pulmonary circulation was obtained in this case of *cor pulmonale*. The innominate and peripheral veins appear normal in size and location



FIG. 10. Contrast Roentgenogram—Left Anterior Oblique Projection at 11 seconds.

Left atrium, left ventricle, thoracic aorta with vessels from arch well opacified. Black arrow near spine indicates left atrium; directly above is large pulmonary vein. Anterior arrow points to left ventricular cavity. Note elliptical density possibly due to stream from left atrium or overlapping of atrio-ventricular densities. Three main branches from aortic arch designated by small arrows. Note "aortic triangle" bounded by left subclavian artery in front, the spine behind, and the arch of the aorta below.

(figures 2, 2A, 6, 6A, 9, 9A, 12 and 12A). The superior vena cava also appears to be normal throughout its course (same figures). It begins in front of the second right costal cartilage and passes directly downward forming the right border of the supra-cardiac shadow to end in the right

atrium at the level of the third interspace. It lies well to the right of the ascending aorta midway between the sternum and the spine, and even with the posterior wall of the ascending aorta; it curves gently backward at the level of the pulmonary artery, and then forward again to enter the atrium.

The right atrium (figures 2, 2A, 6, 6A, 9, 9A, 12 and 12A) is normal in size, shape, and position. It is an oval structure lying at the level of the ninth and tenth thoracic vertebrae and resting almost upon the diaphragm. In lateral view of the heart (right oblique view) it lies directly behind and slightly above the inflow tract of the right ventricle from which

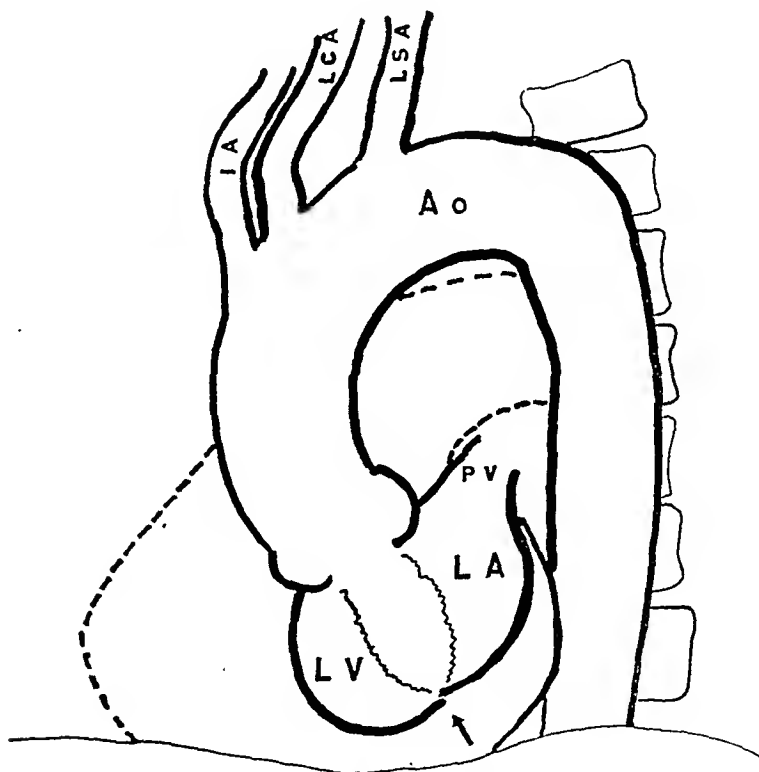


FIG. 10A. *Tracing.*

P. V. = pulmonary vein; L. A. = left atrium; L. V. = left ventricle; Ao. = Thoracic aorta; I. A. = innominate artery; L. C. A. = left common carotid artery; L. S. A. = left subclavian artery.

Black arrow points to density referred to in figure 9.

it is separated by the coronary sulcus (figure 6); it is slightly lower than the left atrium in all views (figures 6, 7, 9, 10, 12, 13). In the postero-anterior position the right atrium lies obliquely behind and to the right of the right ventricle, forming the lower right cardiac border (figure 2). This anatomic relationship is established by the absence of opacification of the atrium in figure 3, while the right ventricle is still outlined. In the left lateral projection (figure 12) the right atrium lies behind the center of the main cardiac shadow.

The right ventricle is enlarged in all diameters and its wall is moderately thickened (5 mm.). It is a roughly triangular cavity having a horizontal inflow tract which extends from the tricuspid orifice to the apex of the chamber; and a vertical outflow tract which reaches from the apex to the



FIG. 11. *Conventional Roentgenogram—Left Lateral Projection.*

Note transverse enlargement of heart obliterating retrosternal space. Anterior border of pulmonary artery and left branch poorly outlined. Aorta appears moderately enlarged and its arch widened.

pulmonary orifice and ends as the conus arteriosus.^{20, 21} Study of this chamber emphasizes the necessity for end and lateral views of the heart if a clear understanding of its anatomy and pathology during life is to be obtained. In the frontal position of the chest (figures 2, 3) there is fore-

shortening of the inflow tract and overlapping by the outflow portion, producing distortion and poor definition. Although the left lateral position of the chest (figure 12) gives a clearer picture of the structure of this ventricle and its relationships, there is still foreshortening and superimposition of structures. However, in the right oblique position (figure 6) which gives a side view of the heart, the right ventricular design is clearly shown. Both inflow and outflow tracts are seen without distortion and appear to be enlarged. The widened conus arteriosus plays but a minor rôle in the formation of the prominent pulmonary arc in this case (figure 6), since it forms only the lowest 2 cm. of that shadow.

The third dimension of the right ventricle is provided by the left oblique position which gives an end view of the heart in which the right chambers lie to the right, and the left atrium and ventricle to the left of the ventricular septum. On each side the ventricle lies in front and the atrium behind (figure 9). In this view the inflow tract, lying near the diaphragm, appears as a rounded body, since its long axis is directed toward the film and it is thus seen in cross section. There is marked enlargement of this cavity and only moderate thickening of its wall. The vertical outflow tract lying next to the film connects the near end of the inflow tract with the pulmonary artery above, and appears to be enlarged in length and breadth. Its terminal portion, the conus arteriosus, is widened but does not reach to the border of the heart as the right auricula forms the silhouette at this point. The thickness of the wall of the outflow tract can only be seen in the lateral projection (figure 12) in which the outflow tract forms the anterior border of the heart. Although the moderate increase in thickness of the right ventricular wall might lead one to conclude that little hypertrophy was present,³⁹ we believe that there must be a considerable increase in the mass of the right ventricle since this moderate thickening of the wall is accompanied by a conspicuous enlargement of the cavity and its surface area. The cusps of the pulmonary valve which can be seen in part in the frontal and both oblique views indicate with certainty the line of demarcation between the conus arteriosus and the pulmonary artery.

The pulmonary artery can be seen as a short broad tube which begins behind the interspace between the third and fourth left costal cartilages and, while curving slightly upward, passes directly backward toward the spine to bifurcate in front of the body of the seventh thoracic vertebra into its right and left branches (figures 2, 3, 6, 9, 12). The pulmonary sinuses lie just above the pulmonary valve and are visible in all projections except the frontal. The diameter of the pulmonary artery in this patient is strikingly enlarged, although there is no appreciable increase in its length. In the frontal view, part of its prominence, however, is due to elevation and displacement toward the left side by the enlarged right ventricle and part to the shadow of its left branch which caps that of the main artery and blends with it (figures 2, 3). Since the pulmonary artery passes directly posteriorly, it is seen best in the lateral position (figure 12).

Both right and left main branches can be seen in all positions but most distinctly in the oblique projections in which they are seen in end and side view. The left branch arches slightly upward from its origin and then passes posteriorly and downward to divide at the left hilum into superior



FIG. 12. *Contrast Roentgenogram—Left Lateral Projection at 4.5 seconds.*

Superior vena cava, right atrium, right ventricle, pulmonary artery, and both main trunks outlined. Black arrow indicates junction of right atrium and right ventricle which are partially superimposed. Directly to the right is inferior vena cava and immediately above is right atrium. Right ventricle lies anteriorly, the wall of the outflow tract indicated by white arrow. Conus arteriosus and pulmonary valves lie above. Note position of pulmonary arterial branches.

and inferior branches; whereas the right branch goes slightly downward and backward but predominantly transversely to end at the right hilum by dividing into two major branches. These vessels are all enlarged. Attention has already been called to the characteristic narrowing and diminution of the

smaller arterial branches seen in the middle and outer zones (figure 3). The pulmonary veins appear rather small and decreased in number but otherwise are not remarkable in this study. They are not seen to advantage, as figure 4, the frontal position, shows the contrast substance has already traversed these vessels. The veins, however, may be seen converging toward both sides of the superior pole of the left atrium (figure 7).

The left side of the heart requires little comment. The left atrium appears to be entirely normal. The left ventricular wall, however, lies at the

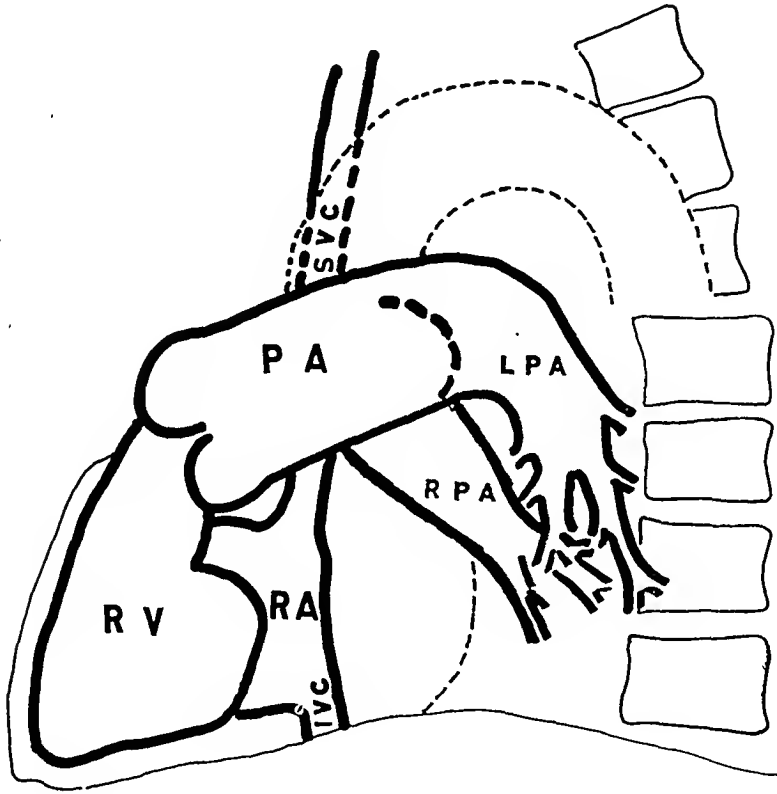


FIG. 12A. *Tracing.*

S. V. C. = superior vena cava; R. A. = right atrium; I. V. C. = inferior vena cava; R. V. = right ventricle; P. A. = pulmonary artery; R. P. A. = right pulmonary artery; L. P. A. = left pulmonary artery.

Note excellent definition of pulmonary artery seen here in side view; and relationship of right and left branches.

upper limit of normal thickness (figures 4, 10) and the ventricular cavity is slightly enlarged (figure 10) but there is no abnormal development of the left ventricular contour (figures 4, 10). This moderate degree of hypertrophy is probably due to coronary artery disease⁴⁴ or chronic myocardial anoxemia² since arterial hypertension can be excluded as a factor. The double border near the apex remains a puzzle (figure 4). The innermost contour appears to be continuous with the inner surface of the left ventricle while the middle curve almost bisects the wall. It is possible that there is a circumscribed thinning of the ventricular wall at this point due to a previous

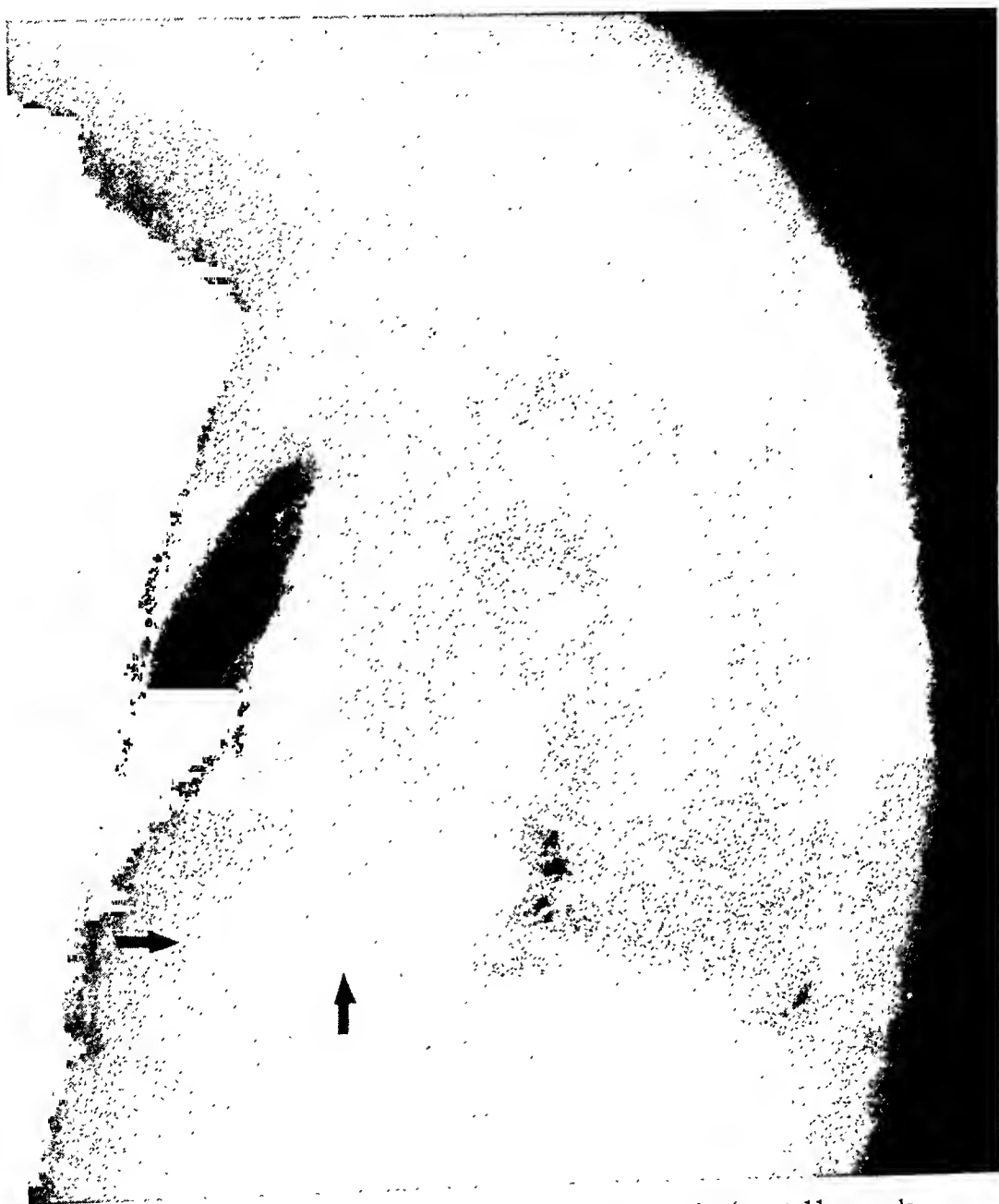


FIG. 13. *Contrast Roentgenogram—Left Lateral Projection at 11 seconds.*

Left atrium, left ventricle, and thoracic aorta opaque. Inferior arrow points to overlapping area of atrium and ventricle. To right lies atrium with vein entering superior pole, to left is left ventricle, and between them a denser shadow possibly caused by blood flowing through mitral valve or overlapping of atrio-ventricular densities. Anterior arrow shows extent of ventricular cavity; immediately above is aorta with dilated sinuses. Note excellent view of aortic sinuses in this position.

myocardial infarct, although there is no history to suggest this explanation and no electrocardiographic evidence to support it. Finally, it is possible, although we believe it unlikely, that this extra line of density may be an artefact. The aorta shows only a moderate degree of dilatation and thickening of its wall, and of elongation, tortuosity and "unfolding" in its course through the thorax. The innominate, the left common carotid, and the left subclavian arteries, likewise, are enlarged and tortuous (figures 4, 4A, 10 and 10A). The "aortic triangle"⁵⁰ which is formed by the aortic arch inferiorly and the spine posteriorly is clearly outlined in figure 10, and

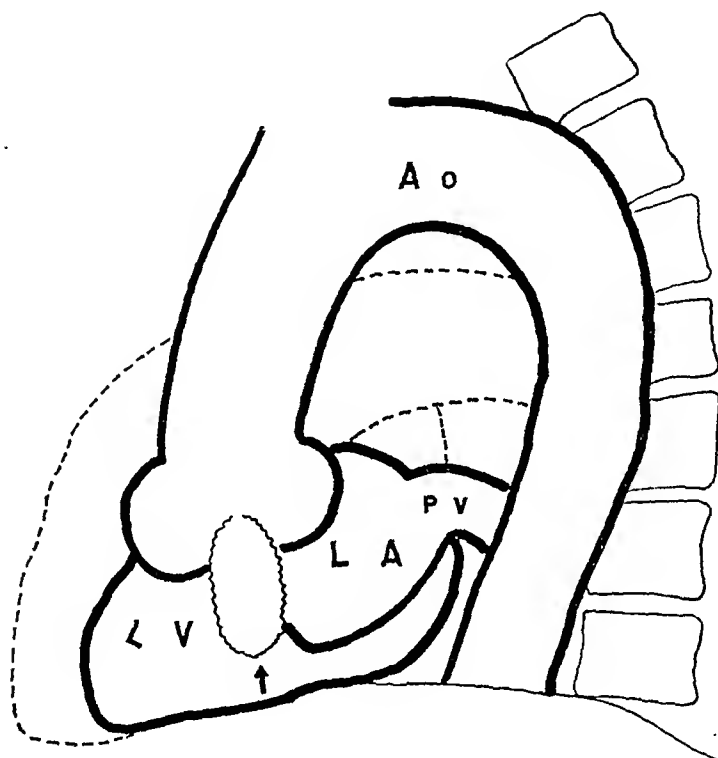


FIG. 13A. Tracing.

P. V. = pulmonary vein; L. A. = left auricle; L. V. = left ventricle; Ao. = aorta. Arrow indicates oval density referred to in figure 13.

its anterior boundary is shown to be the left subclavian artery, a fact heretofore not demonstrated during life.

A comparison of the conventional methods of cardiovascular mensuration and the detailed measurement permitted by visualization leaves no doubt as to the greater worth of the latter method. In this obvious case of *cor pulmonale* the conventional methods, it is true, indicated a moderate degree of cardiac enlargement and considerable dilatation of the pulmonary artery, although accurate evaluation of heart size was impossible since our observations were made with the chest in the full inspiratory position instead of the mid-position used in the establishment of the normal standards.^{25, 47, 48} However, the broad diameter, the transverse diameter, and the frontal area

of the heart were certainly greater than the expected normal value^{47, 48} and the width of the aortic arch and the chord of the aorta lay at the upper limit of the normal.³⁰ Moreover, the pulmonary artery, too, was strikingly enlarged, as indicated by the transverse index of Vaquez and Bordet³⁰ which measured 5.8 cm. as compared with their normal range of 2.7 to 3.2 cm. and the pulmonary "flèche" of Abreu⁴⁹ which was 13 mm. as compared with the normal limits of 1 to 5 mm. Valuable as these data are, they nevertheless give an imperfect picture of the structural state of the heart. Visualization obviates the use of such arbitrary diameters of the cardiac shadow which have no anatomic counterpart, and makes possible the measurement of fundamental anatomic structure such as the height, the width, and the depth of each chamber, the diameter and the length of the larger vessels, and the thickness of the cardiac and the vascular walls. Comparison of these measurements with the normal standard will ultimately permit the precise localization of the disease and accurate estimation of its degree, although at present precise appraisal of each part is impossible since our observations in the normal are yet too limited to permit the establishment of comprehensive standards. However, it is obvious in this case that the right ventricular cavity and wall and the pulmonary artery and its branches are conspicuously larger than any counterpart in our series of normal subjects; whereas the left ventricular wall is only slightly thickened and the thoracic aorta is moderately dilated, elongated, and thickened.

SUMMARY

Visualization of the chambers of the heart and the thoracic blood vessels was performed in a patient with pulmonary heart disease due to chronic bronchitis, pulmonary fibrosis, and emphysema in order to demonstrate the pathological changes occurring in this condition and the value of detailed visualization in its diagnosis. A three dimensional picture of cardiovascular structure and relationships was obtained by study in the frontal, the lateral, and the two oblique positions.

This case study emphasized the well-known fact that pulmonary heart disease cannot be recognized from history, physical signs, or electrocardiographic changes but requires roentgenographic evidence. Conventional roentgen-ray examinations disclosed the typical picture of *cor pulmonale* found in older persons with emphysema and independent heart disease. The enlargement of the right ventricle and the pulmonary artery and its branches was revealed by the prominence of the right lower cardiac border, the pulmonary arc, and the hilar shadows in the frontal view, and by the accentuation of the right ventricular contour, the pulmonary arc, and the right and left pulmonary arteries in the other positions. But conventional roentgenology could not define the boundaries of the right ventricle and the pulmonary artery or show how much these structures entered into the formation of the cardiac silhouette.

Detailed cardiovascular visualization, however, revealed the size, the shape, and the position of each chamber and the diameter and the course of the great vessels and the pulmonary circulation. The superior vena cava and both atria were entirely normal and the left ventricle and the aorta were only moderately enlarged; whereas the right ventricle and the pulmonary artery were conspicuously enlarged. Both inflow and outflow tracts of the right ventricle were involved and showed dilatation of their cavities and thickening of their walls. The conus arteriosus, which was distinguished from the pulmonary artery by the pulmonary valve, played no immediate part in the formation of the prominent pulmonary arc in the frontal view, although it was border forming for a short distance in the right oblique view. The outflow tract appeared to form the entire anterior cardiac border in the lateral view.

The exaggeration of the pulmonary arc in this case is due to two factors: elongation of the right ventricle upward and to the left with displacement of the pulmonary artery in these directions and marked enlargement of this vessel itself. The pulmonary arc is formed exclusively by the pulmonary artery except in the frontal position in which the upper half centimeter of this curve is caused by the arching left branch of this vessel. The accentuation of the hilar shadows is due to enlargement of the main branches of the pulmonary artery and their larger subdivisions while the decrease in lung markings in the mid and outer zones of the lungs is due to narrowing and obliteration of the smaller vessels.

CONCLUSIONS

1. Detailed visualization of the cardiovascular system demonstrated for the first time during life the nature and the extent of the pathological changes in pulmonary heart disease.
2. Cardiovascular mensuration may now become an exact procedure since it can measure fundamental anatomic structures rather than arbitrary diameters having no anatomical counterpart.
3. The recognition of the early stages of pulmonary heart disease which hitherto could not be diagnosed should now be possible.

REFERENCES

1. KOUNTZ, W. B., and ALEXANDER, H. L.: *Emphysema*, Medicine, 1934, xiii, 251.
2. KOUNTZ, W. B., ALEXANDER, H. L., and PRINZMETAL, M.: The heart in emphysema, *Am. Heart Jr.*, 1936, xi, 163.
3. PARKINSON, J., and HOYLE, C.: The heart in emphysema, *Quart. Jr. Med.*, 1937, vi, 59.
4. DYSON, J. M.: The radiologic recognition of heart disease in pneumoconiosis, *Am. Jr. Med. Sci.*, 1933, cxxxvi, 165.
5. DYSON, J. M.: Pulmonary heart disease in pneumoconiosis, *Am. Heart Jr.*, 1934, ix, 764.
6. NEMET, G., and ROSENBLATT, M. B.: Cardiac failure secondary to chronic pulmonary tuberculosis, *Am. Rev. Tuberc.*, 1937, xxxv, 713.
7. WARING, J. J., and BLACK, W. C.: The syndrome of obstruction in the lesser circulation, *Am. Jr. Med. Sci.*, 1934, clxxxvii, 652.

8. AYERZA, L.: *Maladie d'Ayerza sclérose secondaire de l'artère pulmonaire (cardiaques noirs)*, *Semana Méd.*, 1925, i, 43.
9. ARRILLAGA, F. C.: *Sclérose de l'artère pulmonaire secondaire a certains états pulmonaires chroniques*, *Arch. des mal. du coeur*, 1913, vi, 518.
10. GREENSPAN, E. B.: *Carcinomatous endarteritis of the pulmonary vessels resulting in failure of the right ventricle*, *Arch. Int. Med.*, 1934, liv, 625.
11. WYCKOFF, J., and BUNIM, J.: *Observations on an apical diastolic murmur unassociated with valvular disease, heard in cases of right ventricular hypertrophy*, *Trans. Assoc. Am. Phys.*, 1935, i, 280.
12. CLARK, E., and GRAEF, I.: *Chronic pulmonary arteritis in schistosomiasis Mansoni associated with right ventricular hypertrophy*, *Am. Jr. Path.*, 1935, xi, 693.
13. BARNES, A. R., and YATER, W. M.: *Paroxysmal tachycardia and alternating incomplete right and left bundle-branch block with fibrosis of myocardium; failure of right ventricle due to ancient thrombus in pulmonary arteries; fibromyxoma of left auricle occluding mitral orifice and simulating mitral stenosis*, *Med. Clin. North Am.*, 1929, xii, 1610.
14. MEANS, J. H., and MALLORY, T. B.: *Total occlusion of the right branch of pulmonary artery by organized thrombus*, *ANN. INT. MED.*, 1931, v, 417.
15. BOAS, E. P.: *Cardiovascular complications of kyphoscoliosis*, *Am. Jr. Med. Sci.*, 1923, clxvi, 89.
16. RÖSLER, H.: *Zur röntgenologischen Beurteilung des Herzgefäßbildes bei Thoraxdeformitäten [(Kypho)-Skoliose, reine Kyphose, Trichterbrust]. Nebst Bemerkungen über den Ösophagusverlauf*, *Deutsch. Arch. f. klin. Med.*, 1929, clxiv, 365.
17. EDEIKEN, J.: *Effect of spinal deformities on heart*, *Am. Jr. Med. Sci.*, 1933, clxxxvi, 99.
18. PARKINSON, J.: *Enlargement of the heart*, *Lancet*, 1936, i, 1337, 1391.
19. WHITE, P. D.: *Heart disease*, 2nd Ed., 1937, Macmillan, New York.
20. KIRCH, E.: *Das Verhalten von Herz und Kreislauf bei rechtsseitiger (pulmonaler) Herzhypertrophie*, *Würz. Abhandl. a. d. Gesamtgeb. d. prakt. Med. (New Series No. 2)*, 1925, xxii, 73.
21. KIRCH, E.: *Pathogenese und Folgen der Dilatation und der Hypertrophie des Herzens*, *Klin. Wchnschr.*, 1930, ix, 669, 817.
22. MOSHCOWITZ, E.: *Hypertension of the pulmonary circulation*, *Am. Jr. Med. Sci.*, 1927, clxxiv, 388.
23. WEISS, S., and BLUMGART, H. L.: *The velocity of the blood flow and its relation to other aspects of the circulation in patients with emphysema*, *Jr. Clin. Invest.*, 1927, iv, 555.
24. RICHARDS, D. W., CAUGHEY, J. L., COURNAND, A., and CHAMBERLAIN, F. L.: *Intravenous saline infusion as a clinical test for right-heart and left-heart failure*, *Trans. Assoc. Am. Phys.*, 1937, lii, 250.
25. DIETLEN, H.: *Orthodiographische Untersuchungen über pathologische Herzformen und das Verhalten des Herzen bei Emphysem und Asthma*, *München. med. Wchnschr.*, 1908, lv, 1770.
26. GROEDEL, F. M.: *Die Röntgendiagnostik der Herz- und Gefässerkrankungen*, Berlin, 1912. Verlag von Hermann Meusser.
27. STAHLIN, R.: *Pathologie, Pathogenese und Therapie des Lungenemphysems*, *Ergebn. d. inn. Med. u. Kinderh.*, 1915, xiv, 516.
28. LUTEMBACHER, R. V.: *Syndrome tricuspidien terminal dans les lesions chroniques du poumon*, *Arch. d. mal. du coeur*, 1916, ix, 141.
29. DIETLEN, H.: *Das Herz bei Emphysem und Bronchialasthma. Herz und Gefäße in Röntgenbild*, Leipzig, 1923.
30. VAQUEZ, H., and BORDET, E.: *Radiologie du coeur et des vaisseaux de la base*, 4th Ed., 1928, J. B. Bailliere et Fils, Paris.
31. ASSMAN, H.: *Die klinische Röntgendiagnostik der inneren Erkrankungen*, 5th Ed., 1934, F. C. W. Vogel, Berlin.

32. CLERC, A., and MOURRUT, E.: Bronchite chronique sans cyanose. Lésions probables de l'artère pulmonaire, décelées par le seul examen radiotherapique, Bull. et mém. Soc. méd. d. hôp. de Paris, 1931, 292.
33. ROBB, G. P., and STEINBERG, I.: A practical method of visualization of chambers of the heart, the pulmonary circulation, and the great blood vessels in man, Jr. Clin. Invest., 1938, xvii, 507.
34. ROBB, G. P., and STEINBERG, I.: Visualization of chambers of the heart, the pulmonary circulation, and the great blood vessels in man, Am. Jr. Roentgenol., 1939, xli, 1.
35. ROBB, G. P., and STEINBERG, I.: Visualization of chambers of the heart, the pulmonary artery, and the great blood vessels in the normal; preliminary study. (To be published.)
36. ROBB, G. P., and STEINBERG, I.: Visualization of chambers of the heart, the pulmonary circulation, and the great blood vessels in heart disease; preliminary observations, Am. Jr. Roentgenol. (In press.)
37. STEINBERG, I., and ROBB, G. P.: Mediastinal and hilar angiography in pulmonary disease. A preliminary report, Am. Rev. Tuberc., 1938, xxxviii, 557.
38. STEINBERG, I., and ROBB, G. P.: Identification of the cardiovascular structures in a patient with fibrothorax. The value of contrast roentgenography. Radiology (In press).
39. BRENNER, O.: Pathology of the vessels of the pulmonary circulation, Arch. Int. Med., 1935, lvi, 211, 457, 724, 976, 1189.
40. LAUBRY, C., COTTENOT, P., ROUTIER, D., and HEIM DE BALSAC, R.: Etude anatomo-radiologique du coeur et des gros vaisseaux par opacification, Jr. de Radiol. et d'Electrol., 1935, xix, 193, 561, 700; 1936, xx, 66.
41. NEMET, G.: Some clinical aspects of the radiology of the heart, Med. Clin. North America, 1932, xv, 1383.
42. NEMET, G., and SCHWEDEL, J. B.: Roentgenologic studies of the right ventricle, Am. Heart Jr., 1932, vii, 560.
43. SCHWEDEL, J. B., and EPSTEIN, B. S.: Radiological study of the pulmonary artery with special reference to the main branches, Am. Heart Jr., 1936, xi, 292.
44. RUBIN, E. L.: Visualization of the pulmonary artery by x-rays, Brit. Jr. Radiol., 1937, x, 501.
45. GRAY, H.: Anatomy of the human body, 23rd Edition, 1936, Lea and Febiger, Philadelphia.
46. PALMER, J. H.: The development of cardiac enlargement in disease of the heart: A radiological study, Medical Research Council, Special Report Series No. 222, London, 1937.
47. HODGES, P. C., and EYSTER, J. A. E.: Estimation of the cardiac area in man, Am. Jr. Roentgenol., 1924, xii, 252.
48. HODGES, F. J., and EYSTER, J. A. E.: Estimation of the transverse cardiac diameter in man, Arch. Int. Med., 1926, xxxvii, 707.
49. ABREU, M.: Etudes radiologiques sur le poumon et le mediastin, 1930, Masson et Cie, Paris.
50. PARKINSON, J., and BEDFORD, D. E.: Aortic triangle; radiological landmark in left (or II) oblique position, Lancet, 1936, ii, 909.

UNTOWARD EFFECTS FROM THE USE OF ERGOT AND ERGOTAMINE TARTRATE*

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ERGOT preparations have enjoyed a time-honored place in obstetrical practice. In properly standardized dosage they have come to be accepted as useful oxytocics when administered after expression of the placenta; they promote uterine involution and prevent postpartum bleeding and puerperal sepsis. Since isolation of the crystalline alkaloid, ergotamine, described by Spiro and Stoll¹ in 1921, numerous clinical entities have been treated by the specific ergot alkaloids. At one time in the past decade, approximately 80 medical disorders of one kind or another were enthusiastically treated with ergotamine tartrate. Peptic ulcer, migraine, pruritus, diabetes mellitus and insipidus, hyperthyroidism, glaucoma, various hemorrhagic tendencies, melancholia, epilepsy, and cord bladder of taboparetic origin, all may be mentioned as examples of disease states appearing to respond to this form of medication. The calming effect of time and of a few well-directed clinical and physiologic studies² has gradually hewn this vast array of therapeutic indications in the field of internal medicine down to a very select group of conditions, the chief of which are migraine³ and pruritus.⁴

Amazing controversies have been waged in the medical literature of the past decade as to the fundamental pharmacologic effects of ergotamine. That its effects are significantly different from those of ergotoxine, which was discovered by Barger and Carr⁵ in 1906, can no longer be maintained.⁶ The original and fundamental observation by Barger and Dale⁷ that ergotoxine has a stimulatory effect on smooth muscle holds true in the light of present knowledge, and the same applies to ergotamine. Both drugs are stimulants to the heart, arteries, intestine and uterus. Increases in blood pressure and intestinal peristalsis are thus secondary.⁸ Interesting speculation has arisen over Dale's discovery of "vasomotor reversal," that is, the elevated blood pressure produced by an injection of ergotoxine may be slightly and transiently lowered by an injection of epinephrine. That an important factor in the relief of migraine by ergotamine is its vasoconstricting property has recently been indicated.⁹

A rational explanation for the occasional marked relief obtained in cases of pruritus by the use of ergotamine is not clear. The popular hypothesis heretofore has been that ergotamine partially paralyzes the sympathetic nerve endings whose irritability is responsible for the pruritus. Another explanation for this curious phenomenon of relief suggests itself: It is a well-known clinical observation that any constant pruritus is more severe when there is an increased room temperature and is less severe when there is a

* Submitted for publication April 28, 1938.

decreased room temperature. Cooling lotions frequently also are of assistance. Ergotamine is known to produce a fall in peripheral temperature¹⁰ and to produce decreased peripheral blood flow¹¹ by means of its vasoconstricting power. The converse has been noted, that injection of histamine in cases of atopic dermatitis produces an elevation of the temperature of the flexural surfaces with an associated localized pruritus.¹² All of this suggests that the relief of pruritus by ergotamine is in some way related to its cooling effect on skin temperature.

Barger¹³ has described in great detail the complications that follow the administration of ergot, having traced them through medical history from medieval times. Two types of ergotism have been described: One type, in which peripheral gangrene develops, seems clear cut; the other type, in which so-called epidemic convulsions occur, is not so clear cut. The convulsive type of ergotism originated in famine districts where cereals were the chief source of nutrition, and it was associated with cataracts, massive edema, peripheral skin changes, and psychoses but not with gangrene. Stockman¹⁴ was able to isolate toxic salts of phytic (inosite hexaphosphoric) acid, definite neurotoxins, from several cereals which, when injected hypodermically into monkeys fed on a low vitamin diet, would produce a picture strikingly similar to that known as "convulsive ergotism."

UNTOWARD EFFECTS FROM THE USE OF ERGOT AS RECORDED IN THE LITERATURE

In the modern medical literature there are few reports of cases of toxicity following the use of ergot. Oldright¹⁵ in 1870 described a case in which there were "first, symptoms of spasm of the arterioles with dizziness, syncope and surface coldness followed by congestion of the face and head." Meadows¹⁶ mentioned symptoms of marked depression, nausea, headaches, and swelling of the hands in a case in which the patient was given $\frac{1}{2}$ dram (1.85 c.c.) of powdered ergot. The same dosage was given three weeks later and the same symptoms recurred in an exaggerated form. Later, the same dose produced only mild toxic symptoms. Keating¹⁷ described a case in which through a misunderstanding the patient took $\frac{1}{2}$ dram doses of a fluidextract of ergot every half hour for four hours. Cyanosis, dyspnea, nausea, thready pulse, dilated pupils, and powerful uterine contractions developed, but the patient responded rapidly to circulatory stimulants. Hulme¹⁸ gave one teaspoonful of Squibb's fluidextract of ergot to a 48-year-old woman with menorrhagia. Forty minutes later, the patient's hands, face, and abdomen became swollen, her pulse became rapid, weak, and irregular, the pupils were dilated, and nausea, dizziness, and blurred vision were complained of. Moskowitz's¹⁹ patient, who received 1 dram (3.7 c.c.) of the fluidextract of ergot three times daily to promote postpartum uterine involution, suffered from coldness, cyanosis and weakness of all extremities on the sixth day. While the heart appeared to be normal and the brachial

and femoral arteries were not involved, there was complete absence of pulsations in both radial, popliteal, and dorsalis pedis arteries which persisted for 60 hours after prompt discontinuation of ergot medication. Meanwhile, pain and impending gangrene appeared in each foot and there was some subsequent sloughing of part of one foot. In these five cases the drug was administered for therapeutic purposes and in at least one of the cases, that of Keating, the dosage was larger than that ordinarily given.

Untoward effects from the use of ergot in attempts to produce abortion are especially interesting because of the severity of the symptoms. Davidson²⁰ reported a case of attempted abortion in which two handfuls of powdered ergot had been taken in one dose. Among other symptoms, jaundice of the upper extremities was described. Necropsy revealed numerous hemorrhages in the viscera and small ruptured blood vessels. Kobert²¹ cited four cases of fatal attempts to produce abortion with ergot. He described subcutaneous icterus with sudden blackness and numbness of extremities and subsequent mummification. McKay²² described a case in which the arms became painful and the fingers swollen, painful, and cyanotic and finally gangrenous following the ingestion of a large quantity of liquid ergot in an effort to produce abortion. Amputation of the parts was ultimately necessary. Rosenbloom and Schildecker's²³ patient had become unconscious after attempting abortion with ergot; loss of bowel control, urinary suppression, chronic convulsions, and visible uterine contractions developed. The stools were bloody and contained sloughed intestinal mucosa. Necropsy revealed punctate hemorrhages throughout the intestinal mucous membrane.

UNTOWARD EFFECTS FROM THE USE OF ERGOTAMINE TARTRATE AS RECORDED IN THE LITERATURE

The number of cases in which definite vasospastic phenomena and peripheral gangrene of the type seen in ergotism have occurred and in which ergotamine may be definitely considered as an etiologic factor is not large. These cases may be grouped according to the condition for which ergotamine was given:

Puerperal Sepsis. A considerable number of cases of puerperal sepsis in which ergotamine tartrate was administered and in which gangrene developed has been recorded. Since peripheral gangrene occurs infrequently in puerperal sepsis when ergot is not used, many have discounted the rôle of ergotamine in causing the gangrene. Saenger²⁴ reviewed 13 cases in 1929 and assumed that ergotamine tartrate was not the principal cause of the peripheral gangrene; he concluded that the appearance of gangrene was due in all cases to infectious toxic changes in the vessels. He felt that if ergotamine had played a part it was a secondary one. A review, however, of such cases as the following can lead only to the conclusion that ergotamine has played a significant rôle at least in some of the cases of puerperal sepsis in which gangrene has appeared:

Case 1 (Oginz²⁵). A primipara, aged 19 years, with puerperal sepsis was given 6 drams (22 c.c.) of fluidextract of ergot and a total of 45 c.c. (22.5 mg.) of gynergen subcutaneously over a period of 11 days. On the seventh day postpartum, coldness and cyanosis of the extremities developed, and there was complete disappearance of the radial pulse. The heart action, however, was exceptionally good. By the tenth day the extremities were cold and there was excruciating pain in the right foot; the toes and plantar surface first became blue, then green, and later black. Twenty-four hours after gynergen medication was discontinued, the upper extremities became warmer and the radial pulse returned. Pain in the right foot continued to be severe and a line of demarcation appeared in the right foot on the sixteenth day. The foot improved with baking and local treatment but, four months later, it was necessary to amputate the stumps of the first three toes and probe a discharging sinus in the ball of the foot.

The prompt improvement in the vascular condition following discontinuation of gynergen therapy strongly suggests that the gynergen, and not the puerperal sepsis, was responsible for the accident.

Case 2 (Roch²⁶). A woman, aged 23 years, suffered from chills, fever, and uterine discharge five days after cesarean section. She was given 20 drops of ergotamine tartrate twice daily for four days (total dose estimated to be 10.6 mg.). On the third and fourth days there was painful pallor of all extremities. The arterial blood pressure in millimeters of mercury was 80 systolic and 60 diastolic. On the fifth day the pain became more intense in all extremities, particularly in the left foot. The temperature was 38.7 to 39.5° C., the heart beat was regular and rapid, the pulse not perceptible, and the left foot was extremely painful, with splotchy white and purple discolorations of the anterior third. The toes were cold, violaceous, and had the appearance of impending gangrene; the right foot and both hands had the same general appearance, although the condition was less marked. Next to the livid areas the skin was pale and cold. The patient complained of spontaneous paresis and paresthesias and increased pain to the slightest touch. There was complete anesthesia of the toes of the left foot. Arterial pulsations were not perceptible. It was impossible to determine the blood pressure in the arm, forearm, thigh, or leg. Blood cultures were negative. The diagnosis of ergotism was arrived at by elimination. The patient was treated with spasalgine (containing both papaverine and atropine derivatives) and acetylcholine. The symptoms were ameliorated after 24 hours. On the third day of treatment, the blood pressure could be taken in all four extremities. The extremities appeared to be normal except for the left foot where there was definite gangrene. It was later necessary to amputate a portion of this left foot.

Again the prompt response to the discontinuation of the drug and to the administration of vasodilating drugs points strongly to ergotamine as the cause of the condition.

Case 3 (Polano²⁷). A woman, aged 36, who had tuberculosis showed evidence of uterine infection following a therapeutic abortion performed during the third month of pregnancy. The patient received postoperatively 1 mg. of ergotamine orally three times a day for five days. The radial pulse was not palpable on the seventh day and on the fourteenth day there was definite dry gangrene of the left hand.

The disappearance of the radial pulse prior to the onset of symptoms of ischemia again suggests that the vasospastic action of ergotamine was the first manifestation of the impending gangrene, a circumstance hardly to be expected if the infectious process was responsible.

Menorrhagia. Case 4 (Brack²⁸). A woman, aged 30 years, with marked nervousness and menorrhagia, was given a total of 24 mg. of ergotamine hypodermically over a period of 42 days. On the twenty-fifth day of medication a progressive numbness of all the fingers developed. On the fortieth day the patient complained of severe, knife-like pains and of a withering sensation in her fingers and she was unable to bend them without aid. Small doses of scopolamine and dial partially controlled the symptoms, but they persisted for three weeks after discontinuation of ergotamine medication.

Hyperthyroidism. Case 5 (Schönbauer²⁹). A woman, aged 28 years, suffering from exophthalmic goiter, was given 0.5 c.c. (0.25 mg.) of ergotamine hypodermically twice daily for seven days, with 1 c.c. twice daily on the eighth and ninth days. On the ninth day there were pain and cramping of the lower extremities with swelling and discoloration of the right foot and toes. The toes rapidly became livid, cold, and pulseless, showing absence of pulsation by capillary microscopy. By the fifteenth day the gangrene had become dry and more sharply demarcated.

Case 6 (Platt³⁰). A girl, aged 16 years, with hyperthyroidism was given subcutaneously a total of 20 mg. of ergotamine in 23 days. Administration of ergotamine was promptly discontinued on the appearance of severe muscular cramps of the lower extremities, with coldness, numbness, pain, and cyanosis of the entire right foot and left big toe. Scopolamine, grain 1/150 (0.0004 gm.) by hypodermic injection, produced slight improvement, but the cramps persisted for three weeks.

Case 7 (Speck³¹). A woman, aged 29 years, who had thyrotoxicosis, was given a routine preliminary treatment with ergotamine which consisted of 93 tablets (46.5 mg.). After an interval of three weeks, a second course of ergotamine was instituted. On the sixth day a furry sensation was noted in both legs, and abdominal pain, diarrhea and severe pain and coldness in both legs were noted on the eighth day. The following day the feet were cold, slightly blue and tactile sensation was diminished. Ergot poisoning was suspected and administration of the ergotamine was discontinued. The patient had then received 27 tablets (13.5 mg.) of ergotamine. Despite contrast baths, atropine, and the intravenous injection of theophylline, sodium acetate and sodium nitrite, the appearance of impending gangrene increased to definite demarcation in the lower part of the legs. On the sixteenth day, sensation improved and the feet were warmer. Marked improvement occurred in the next few weeks with a return of blood supply and this Speck attributed to the theophylline. Six months later there were some residual symptoms of stiffness in the right ankle joint and some thickness on the back of the right foot.

Case 8 (Žorn³²). A woman, aged 39 years, suffering from exophthalmic goiter, was given postoperatively 15.5 mg. of ergotamine tablets over a period of eight days. There was sudden development of pain and numbness in both lower extremities on the eighth day. The feet were cold and there was beginning gangrene. Arterial pulsations could not be felt on either side. The patient was treated with contrast baths and 1 c.c. injections of padutin (pancreatic extract) daily for three days. The peripheral pulsations returned and the symptoms cleared entirely.

Case 9 (Müller³³). A woman with Basedow's disease was given 24 c.c. of ergotamine subcutaneously over a period of 18 days and, simultaneously, roentgen treatment over the thyroid gland. On the sixteenth day a violent sensation of pain and coldness developed in both lower extremities. The right foot turned a mottled, purplish color and there was indurated swelling of the lower part of the right leg. The pain and cramps became intense. On the eighteenth day the administration of ergotamine was discontinued. Despite all treatment, dry gangrene with demarcation had involved all toes on the right foot. In the next six months most of the toes dropped off spontaneously, but it was necessary to amputate the right big toe. Pain in the right leg persisted for a total of seven months and then entirely disappeared.

Jaundice and Pruritus. Case 10 (Yater and Cahill³⁴). A man, aged 64 years, suffering from jaundice and severe pruritus, was given 1 c.c. (0.5 mg.) of ergotamine tartrate by subcutaneous injection three times daily for six and a third days (a total of 9.5 mg.). On the second day of administration; coldness was noted in the upper extremities. By the fourth day there was coldness and blueness of the distal third of both feet. Two days later symptoms were much more definite; faint pulsations were felt in the dorsalis pedis arteries. There was definite gangrene of the toes of both feet on the thirteenth day. Bilateral amputation of the distal portions of both lower extremities was performed one month after the onset of the gangrene. The extremities were studied arteriographically and pathologically.

Case 11 (Gould, Price, and Ginsberg³⁵). A woman, aged 52 years, suffering from jaundice and pruritus, was given 0.5 c.c. (0.25 mg.) of ergotamine tartrate, subcutaneously, daily for four days (a total of 1 mg.). After the second ampoule, pain and coldness developed in the legs. On the third day cyanosis, coldness, and impaired sensation of the lower two-thirds of both legs developed. On the fourth day, pulsations of the dorsalis pedis and radial arteries could not be felt. A blood pressure reading could not be obtained. The heart sounds were regular and of fair quality. Examination of the ocular fundi showed arterial narrowing which was not present at the time of admission. Despite the administration of glyceryl trinitrate and amyl nitrite the lower two-thirds of the legs became gangrenous. The patient became semistuporous and died on the following day. At necropsy all the arterioles examined were found to be contracted.

Case 12 (Perlow and Bloch³⁶). A 36-year-old man with Hodgkin's disease, jaundice, and pruritus was given 1 mg. of ergotamine by mouth and 2.5 mg. subcutaneously over a period of six days. On the evening of the last injection there was pain in the toes, and the next day morphine was required for relief of increasing pain in the toes. The toes were cyanotic, cold, and slightly ischemic. On the following day pulsations could not be felt in either the dorsalis pedis or posterior tibial arteries. The peripheral skin temperatures were markedly decreased. Several injections of papaverine hydrochloride, $\frac{1}{2}$ grain (0.032 gm.) intravenously caused a rapid return of the feet to a normal appearance with normal peripheral arterial pulsations and skin temperature.

Other Conditions. Vascular accidents other than thrombosis of the peripheral vessels and gangrene have been described. Labbé, Boulin, Justin-Besançon, and Gouyen³⁷ described a case of Basedow's disease in which three subcutaneous injections of ergotamine produced, first, an attack of anginal pain and, later, hemiplegia. Zimmermann³⁸ described a prolonged fatal anginal attack occurring a few minutes after injection of one ampoule of ergotamine and he reviewed the effect of gynergen on the heart. He has also described a case of toxic goiter in which ergocholine produced auricular fibrillation, lasting from a few minutes to two hours, and with a ventricular frequency from 150 to 170. The patient had definite evidence of diffuse myocardial damage. The toxic symptoms described by Panter³⁹ were unusual: in his case tinnitus, absence of deep reflexes, and fixed pupils persisted for a week after ergotamine therapy (nine ampoules having been given in three days). Baber and Tietz's⁴⁰ patient died after having received 2 mg. of ergotamine daily for three days. Pulmonary infarctions were found in this case.

UNTOWARD EFFECTS FROM THE USE OF ERGOTAMINE TARTRATE AT THE MAYO CLINIC

The following two cases in which untoward symptoms developed from the use of ergotamine tartrate were personally observed by us:

Case 1. A woman, aged 59 years, registered at the clinic October 1, 1934 complaining of painless jaundice and pruritus. A diagnosis was made of partial obstruction of the common duct due to stricture. The jaundice was marked. The systolic blood pressure in millimeters of mercury was 160 and the diastolic 90. General physical examination otherwise gave essentially negative results as did examinations of the urine (except for bile), blood, and serologic test for syphilis.

The patient was hospitalized on October 3. Ergotamine tartrate in oral doses of 1 mg. three times a day, was prescribed for the pruritus and this symptom was controlled after the first two days of medication. A 10 per cent solution of glucose in amounts of 1,000 c.c., and 10 per cent calcium chloride, in amounts of 5 c.c., were given intravenously on the fourth, fifth, sixth, and seventh days. On October 4, the bleeding time was four minutes, the coagulation time (Lee and White) three and a half minutes, and the concentration of bilirubin in the serum 20 mg. per 100 c.c.; the van den Bergh reaction was direct. It is worthy of note that local venous thrombosis occurred with the injections on October 5 and 6.

On October 10, the condition of the patient had markedly improved. The concentration of bilirubin in the serum had dropped to 11 mg. per 100 c.c.; the bleeding time was unchanged, whereas the coagulation time had decreased to two minutes, an abnormally low figure for a patient so deeply jaundiced. Surgical intervention was planned; however, about noon, the patient complained of pain and numbness in her right hand which had become quite blue. The extremities were cold, and the patient was unable to recognize tactile or thermal stimuli applied to the right hand. The administration of ergotamine tartrate, of which a total of 23 mg. had been given, was then discontinued at the onset of these symptoms. The application of local heat to the extremities was followed by apparent improvement. That evening, however, the patient's condition became worse. She was restless, apprehensive, and weak. All four extremities were cold. The cyanosis of the right hand and wrist had become more marked, and the patient could not move the fingers of the right hand. Pulsations could not be felt in the left ulnar or in the right radial and ulnar arteries, and only slightly in the left radial artery. The pulsations of both brachial arteries appeared to be normal, but pulsations of the arteries of the feet were weak. Blood pressure readings could not be obtained in the arms. The cardiac impulses definitely increased in intensity.

The next morning, the patient still complained bitterly of pain in both hands and arms. The color of the right hand remained unchanged. Arterial pulsations had entirely disappeared below the level of the elbow in each arm and were felt with difficulty in the vessels of the feet. It looked as if gangrene of the right hand would develop (figure 1). Continuous, hot, moist packs were applied, however, and massage in the direction of the hands was done for 15 minutes of each hour. Ephedrine, grain $\frac{3}{4}$ (0.05 gm.) was given every two hours.

The patient was fairly comfortable during the night, but on the morning of October 12 looked drowsy and vomited. The condition of the extremities remained the same. The treatment was then altered. The extremities below the elbows were wrapped in cotton batting. The hands were kept slightly lowered and the patient was given 15 c.c. of alcohol every four hours. Venous cyanosis but no arteriospasm was found on examination of the ocular fundi. On October 13 some improvement was noted. There was little, if any, change in the condition of the right hand, but pulsations could be felt in the left radial artery. The patient stopped vomiting and ate a little breakfast.

On October 14, pulsations could be felt in all the vessels of the upper extremities and pulsations in the feet were much more easily felt. The purplish discoloration of the right hand had largely disappeared and the temperature of both hands appeared to be normal. Blood pressure readings were obtained for the first time, the systolic blood pressure being 118 and the diastolic 84. The pulse rate was 80 beats per minute. The temperature rose to 100° F. and an edematous swelling of the right hand appeared.

By October 15 further improvement was noted. The dorsum of the right hand and wrist was edematous and dusky (see figure 1). The bleeding time was two



FIG. 1. (Case 1). Photograph taken October 15, 1934 during the height of the brawny edematous swelling of the right hand.

minutes, the coagulation time was still unchanged. By October 19 the jaundice had cleared perceptibly. The value for serum bilirubin was 3 mg. Tactile sensibility was diminished grade —3 to —4, and pain perceptibility, grade —1 to —2 (on a basis of 1 to 4) over most of the surface of the right hand. The movements of the fingers of the right hand were markedly diminished in range and speed, those of the wrist less so. By October 22, the patient's condition had improved so much that she was permitted to return home.

Soon after this the jaundice reappeared and the patient returned to the clinic on December 7. Her right hand was still stiff, and muscular atrophy (grade 2) and

paresthesias were present (figure 2). The coagulation time had increased to four and a half minutes. A diagnosis was again made of partial obstruction of the common duct due to stricture and of post-thrombotic contraction with atrophy of the right hand. Exploration was carried out on December 10. A stricture of the common duct, apparently 2 cm. in length, was found, excised, and an end-to-end anastomosis was made between the hepatic and common ducts. The postoperative convalescence was uneventful. Further improvement in the condition of the right hand followed persistent physiotherapy (see figure 2).

Case 2. A woman, aged 50 years, first registered at the clinic on May 21, 1934 at which time a radical left mastectomy was performed for adenocarcinoma, grade 3, which measured 3 cm. in diameter. The lymph nodes were found to be involved. A year later simple amputation of the right breast was performed for diffuse mastitis. The patient last registered at the clinic on January 20, 1936, complaining of jaundice

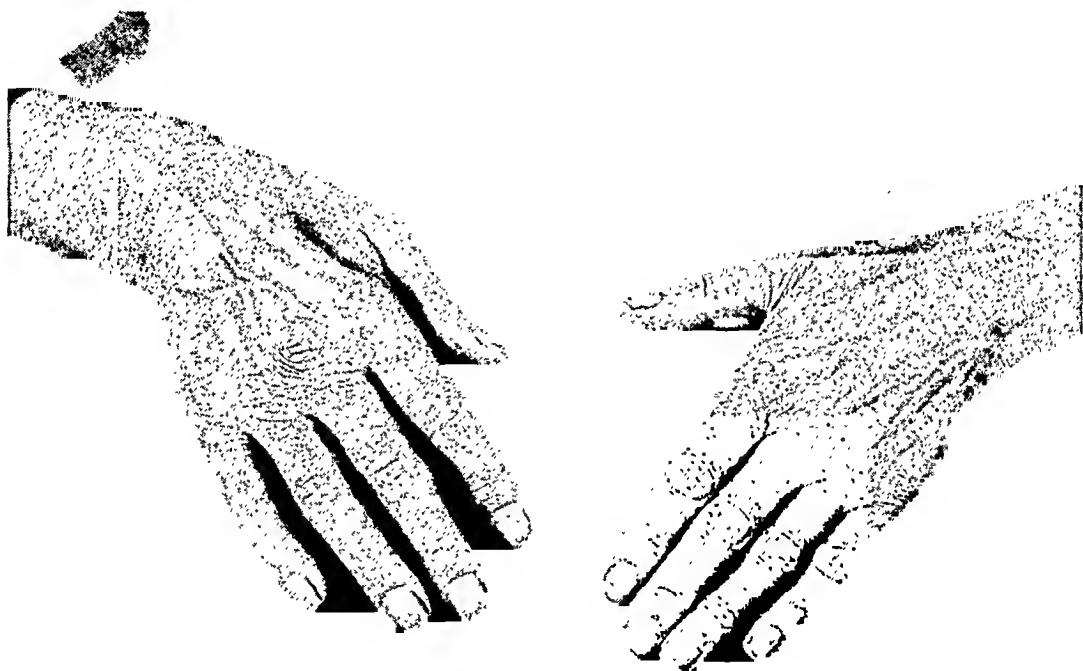


FIG. 2. (Case 1). Photograph taken December 28, 1934 showing residual atrophy of the right hand.

which had come on painlessly about a month previously. Pruritus was marked and the patient was hospitalized for examination. One to three tablets of ergotamine tartrate daily controlled the pruritus. A diagnosis of metastatic carcinoma of the liver was made. On January 28, the radial pulses could be palpated only with the greatest difficulty and the administration of ergotamine tartrate, of which 16 mg. had been given, was discontinued. On the next day the pulses became more easily palpable although they were still small in volume. On the second day after administration of the ergotamine tartrate had been discontinued both radial pulses returned to their normal full volume.

The cumulative toxic, vasoconstrictive action of ergotamine tartrate is well illustrated in these two cases. In the first case, vasoconstriction was followed by thrombosis, ischemic neuritis, and late secondary contracture.

In the second case, vasoconstriction was the sole manifestation of toxicity. In each case the administration of ergotamine tartrate was discontinued as soon as toxic symptoms developed and recovery followed, prompt recognition of the nature of the condition and prompt institution of treatment undoubtedly being responsible for the excellent recovery in each case. In the first case vasodilating drugs contributed to the recovery.

Experience in these two cases led us early to adopt the practice of routine palpation of the arteries of the extremities several times daily during the administration of ergotamine tartrate and in this way further unhappy experiences have been avoided. In this connection, it is interesting that Gaysinovich⁴¹ and his coworkers who have had a wide experience with ergot poisoning resulting from the ingestion of ergot-infested rye bread, have noted a pregangrenous state capable of complete regression, similar to that in these two cases.

The first case was unusual in another respect. In this case tests of coagulation of the blood showed a tendency to rapid coagulation instead of slowed coagulation, as one would expect in the case of a deeply jaundiced patient. It is interesting that the coagulation time was decreased during treatment with ergotamine tartrate and that thrombosis finally occurred. The effect of ergotamine on the coagulation time of the blood in this case is not clear.

GENERAL CONSIDERATIONS

Dosage. Untoward effects sometimes occur after the administration of very small doses of ergot or ergotamine tartrate. Hulme reported toxic symptoms after a teaspoonful of fluidextract of ergot had been given. In Gould, Price, and Ginsberg's case, toxic symptoms appeared soon after the hypodermic administration of a second daily dose of 0.25 mg. of ergotamine tartrate. Only an idiosyncrasy to the drug can explain such effects. Most untoward reactions, however, occur after larger doses and apparently result from a cumulative action of the drug. When ergotamine has been given hypodermically, untoward effects have occurred following doses varying anywhere from 0.5 to 24 mg. When the drug has been given orally, the total amount of the drug administered is somewhat larger and has varied between 10 and 60 mg. In Speck's case the patient tolerated a course of ergotamine therapy consisting of 93 tablets (46.5 mg.) but, after an interval of three weeks, marked vascular symptoms developed after only 13.5 mg. of ergotamine tartrate had been given. That the sensitivity of the individual to ergotamine varies widely is emphasized by the fact that some patients have taken the drug in the usual doses over periods of weeks and even months without untoward symptoms developing, others require two or three times the usual dosage if therapeutic results are obtained, and still others have developed symptoms of ergotism following only small doses of the drug.

Contraindications. Many who have written on obstetrical subjects have expressed the belief that ergot is contraindicated in sepsis. Caffier⁴² be-

lieved that puerperal infection produced toxic injury of the blood vessels and that ergot might produce gangrene more readily in the presence of these changes. The histologic studies of Lewis and Gelfand⁴³ have shown that peripheral vascular thrombosis rapidly follows the intimal damage of ergot. It does not seem unreasonable that thrombosis and gangrene should occur more frequently when two conditions capable of producing intimal damage and thrombosis are active simultaneously.

The untoward effects described by Labbé, Boulin, Justin-Besançon, and Gouyen, and Zimmermann emphasize the danger of administering ergot to individuals who have cardiac disease. Its administration is also thought to be contraindicated in the presence of vascular disease.

Symptoms. The earliest symptoms of ergotism are headache, nausea, vomiting, diarrhea, tinnitus and vertigo. These are the untoward symptoms that have followed the hypodermic injection of ergotamine tartrate in cases of migraine and, when they occur, indicate that smaller doses may be used effectively. Dilatation of the pupils and blurring of vision are also toxic symptoms, and in cases of poisoning by massive doses, unconsciousness and incontinence or suppression of urine, convulsions, sloughing of intestinal mucosa, and bloody diarrhea have been described. Jaundice and cyanosis occur infrequently.

In those cases in which vasospastic phenomena develop the earliest finding is disappearance of the pulse, as in Polano's and our second case. Pain, particularly muscular cramping, peripheral paresthesia, decreased skin temperature, and perhaps pallor (as in the case of Breck) are followed by the appearance of cyanosis, discoloration of the skin, and actual thrombosis; gangrene is a still later development. Cerebral and gastrointestinal symptoms may develop simultaneously with the peripheral vascular condition. Closure of the vessels, with cyanosis, apparently may take place suddenly. If gangrene does not develop, the condition may regress, leaving contracture of the muscles. If gangrene develops spontaneously, amputation of the affected part may occur or surgical amputation may eventually become necessary.

Diagnosis. It is most important to emphasize that the approach of ergotism should be suspected as soon as the pulsation of the vessels diminishes perceptibly in the case of any person receiving ergot or ergotamine. The diagnosis should be clear as soon as any of the peripheral pulses disappears or as soon as paresthesias, pallor, or cyanosis develop.

Prognosis. Of the 14 cases of ergotism following the use of ergotamine which have been reported, gangrene occurred in seven and death in one. The prognosis seems to depend to some extent on what stage the process has reached when it is recognized and when administration of the drug is discontinued. It is significant that gangrene developed in only two of the eight cases in which the administration of ergotamine tartrate was discontinued as soon as the symptoms or local findings attracted the physician's attention. In contrast to the comparative rarity of gangrene under these

circumstances was the development of gangrene in five of six cases in which the administration of ergotamine tartrate was continued after symptoms or local changes had occurred. Gangrene does not necessarily follow the appearance of cyanosis. In four cases administration of the drug was discontinued after the affected parts had become discolored. Ischemic neuritis and contracture of the muscles may persist after the circulation is re-established.

Treatment. Prophylactic measures are several in number: (1) the avoidance of the use of ergot in sepsis and cardiac or vascular disease; (2) its administration only under the close supervision of a physician; (3) awareness on the part of both the physician and patient of early toxic manifestations; (4) careful daily observation of the size of the peripheral vessels while the patient is receiving ergot or its derivatives, and (5) discontinuation of the use of the drug when the pulsations of the vessels perceptibly diminish and on the appearance of the first untoward and bizarre symptoms of muscular cramping or paresthesia.

Vasodilating drugs are indicated as soon as the first symptoms of ergotism appear. Gaysinovich recommended 1 c.c. of 1 per cent pilocarpine solution subcutaneously for its fast dilating effect in addition to the use of daily intravenous administration of 15 to 20 c.c. of 3 per cent magnesium sulfate solution. Rubin and Rapoport's⁴⁴ experience with magnesium sulfate parenterally in the control of hypertension and gangrene induced by the administration of ergotamine likewise points to the value of this drug in the treatment of ergotism. Acetylcholine, as suggested by Roch, might prove helpful. Alcohol⁴⁵ is an effective vasodilator, particularly of the vessels of the upper extremities, and is a helpful sedative in this condition. Papaverine,⁴⁶ in doses of $\frac{1}{3}$ to $\frac{1}{2}$ grain (0.02 to 0.032 gm.) is a well-known and a usually effective vasodilator, especially when given intravenously, and may provide some analgesia. Cleansing enemas should be given when ergotamine has been given orally. The rationale of giving scopolamine, epinephrine, and ephedrine is open to question.

SUMMARY AND CONCLUSIONS

Untoward effects from the use of one of the preparations of ergot or of ergotamine tartrate hitherto reported in the literature have been briefly reviewed. To these we have added two cases personally observed by us in which untoward effects developed following the use of ergotamine tartrate for the control of pruritus.

Some of the untoward effects that have been reported have followed administration of doses larger than those compatible with good practice. In other cases, however, such effects have followed the use of very small doses and have apparently been dependent on the existence of an individual idiosyncrasy to the drug. In still other cases such untoward effects have followed the use of the drug in the usual dosages and were apparently due to a cumulative action of the drug.

In spite of these many instances of ergotism it is not our intention to discourage administration of ergotamine tartrate in doses of proper size provided adequate precautions are taken. The drug has proved itself too valuable for this, especially in the control of pruritus and migraine. Instead, we would emphasize the contraindications to its use, the danger of the development of ergotism, and point out that the onset of ergotism may be suspected early by frequent examination of the arteries of the extremities for spasm and by recognition of its early symptoms.

Prompt and early recognition of ergotism and the discontinuation of ergot or ergotamine tartrate medication, followed by the administration of such vasodilating drugs as pilocarpine subcutaneously, magnesium sulfate parenterally, and alcohol orally, are the prerequisites for the avoidance of irreparable damage.

REFERENCES

1. SPIRO, K., and STOLL, A.: Ueber die wirksamen Substanzen des Mutterkorns, Schweiz. med. Wchnschr., 1921, li, 525-529.
2. FARRAR, G. E., JR., and DUFF, A. M., JR.: Ergotamine tartrate: its direct hyperglycemic action and its influence on the hyperglycemia produced by epinephrine in normal unanesthetized dogs, Jr. Pharmacol., 1928, xxxiv, 197-202.
- YOUMANS, J. B., and TRIMBLE, W. H.: Experimental and clinical studies of ergotamine. I. Effect of ergotamine on the blood sugar and epinephrine hyperglycemia in trained unanesthetized dogs, Jr. Pharmacol. and Exper. Therap., 1930, xxxviii, 121-132. II. The effect of ergotamine on the heart rate of trained, unanesthetized dogs, Jr. Pharmacol. and Exper. Therap., 1930, xxxviii, 133-144. III. The effect of ergotamine on the oxygen consumption of normal, trained dogs, Jr. Pharmacol. and Exper. Therap., 1930, xxxix, 201-208.
- YOUMANS, J. B., TRIMBLE, W. H., and FRANK, HELEN: Experimental and clinical studies of ergotamine. IV. The effect of ergotamine on the basal metabolism, circulation and blood sugar of normal persons and of patients with thyrotoxicosis, Arch. Int. Med., 1931, xlvii, 612-632.
- YOUMANS, J. B., TRABUE, CHARLES, BUVINGER, R. S., and FRANK, HELEN: Experimental and clinical studies of ergotamine. V. The action of ergotamine on the sympathetic nervous system stimulated by epinephrine. Studies of the metabolic rate, pulse rate, blood pressure, blood sugar and the total leukocyte count, ANN. INT. MED., 1933, vii, 653-663.
- LAWRENCE, R. D.: The effect of ergotamine on carbohydrate metabolism and on the stomach, Brit. Jr. Exper. Path., 1930, xi, 145-148.
3. LENNOX, W. G., and VON STORCH, T. J. C.: Experience with ergotamine tartrate in 120 patients with migraine, Jr. Am. Med. Assoc., 1935, cv, 169-171.
- LENNOX, W. G., and LEONHARDT, HILDEGARDE C.: The flow and concentration of blood as influenced by ergot alkaloids and as influencing migraine, ANN. INT. MED., 1937, xi, 663-670.
4. LICHTMAN, S. S.: Therapeutic response to ergotamine tartrate in pruritus of hepatic and renal origin, Jr. Am. Med. Assoc., 1931, xcvii, 1463-1464.
- SNELL, A. M., and KEYS, H. C.: Pruritus of jaundiced patients: its incidence and treatment, Med. Clin. N. Am., 1933, xvi, 1455-1470.
5. BARGER, G., and CARR, F. N.: Quoted by Barger, George.
6. DALE, H. H., and SPIRO, K.: Die wirksamen Alkaloide des Mutterkorns, Arch. f. exper. Path. u. Pharmacol., 1922, xcv, 337-350.
- BURN, J. H., and ELLIS, J. M.: Quoted by Barger, George.

- LOZINSKI, E., HOLDEN, G. W., and DIVER, G. R.: The relative activity of ergotoxine and ergotamine, *Jr. Pharmacol. and Exper. Therap.*, 1931, xlii, 123-131.
- VARTIAINEN, A.: The action of ergoclavine and sensibamine, *Jr. Pharmacol. and Exper. Therap.*, 1935, liv, 259-264.
7. BARGER, G., and DALE, H. H.: Ergotoxine and some other constituents of ergot, *Biochem. Jr.*, 1907, ii, 240-299.
 8. WOOD, H. C., and LA WALL, C. H.: The dispensatory of the United States of America. Ergota., 1937, Ed. 22, J. B. Lippincott Company, Philadelphia, p. 432.
 9. POOL, J. L., and NASON, G. I.: Cerebral circulation: XXXV. The comparative effect of ergotamine tartrate on the arteries in the pia, dura and skin of cats, *Arch. Neurol. and Psychiat.*, 1935, xxxiii, 276-282.
 10. RIGLER, RUDOLF, and SILBERSTERN, ERNST: Über die Temperatursenkende Wirkung des Ergotamins, *Klin. Wchnschr.*, 1926, v, 1831.
 11. ABRAMSON, D. I., and LICHTMAN, S. S.: Influence of ergotamine tartrate upon peripheral blood-flow in subjects with liver disease, *Proc. Soc. Exper. Biol. and Med.*, 1937, xxxvii, 262-267.
 12. WILLIAMS, D. H.: Personal communication to the authors.
 13. BARGER, GEORGE: Ergot and ergotism, 1931, Gurney and Jackson, London, 279 pp.
 14. STOCKMAN, RALPH: The cause of convulsive ergotism, *Jr. Hyg.*, 1934, xxxiv, 235-241.
 15. OLDRIGHT, G. S.: Quoted by Hulme, Laure.
 16. MEADOWS, J.: Quoted by Hulme, Laure.
 17. KEATING, J. M.: Ergot-poisoning, *Med. Rec.*, 1880, xviii, 318-319. The toxic action of ergot, *Med. Rec.*, 1880, xviii, 558-559.
 18. HULME, LAURE: Case of acute ergotism occurring after the ingestion of a fluidounce of the fluid extract of ergot, *Med. News*, 1887, li, 538-540.
 19. MOSKOWITZ, H. L.: Report of a case of ergot poisoning postpartum, *Am. Jr. Obst. and Gynec.*, 1928, xv, 549-552.
 20. DAVIDSON, A.: Fatal case of poisoning by ergot of rye, *Lancet*, 1882, ii, 526-527.
 21. KOBERT, R.: Ueber die Bestandtheile und Wirkungen des Mutterkorns, *Arch. f. exper. Path. u. Pharmacol.*, 1884, xviii, 316-380.
 22. MCKAY, W. J. S.: Gangrene of the fingers following the administration of liquid ergot, *Brit. Med. Jr.*, 1906, ii, 365.
 23. ROSENBLOOM, JACOB, and SCHILDECKER, C. B.: The successful isolation of ergotinin crystals from certain organs in a case of acute ergot poisoning, *Jr. Am. Med. Assoc.*, 1914, lxiii, 1203-1204.
 24. SAENGER, HANS: Über Puerperalgangrän bei septischen Zuständen und Gynergenmedikation, *Zentralbl. f. Gynäk.*, 1929, liii, 586-594.
 25. OGINSZ, PHILIP: Ergotismus gangrenosus, *Am. Jr. Obst. and Gynec.*, 1930, xix, 657-664.
 26. ROCH, M.: Ergotisme gangreneux, *Presse méd.*, 1935, xliii, 31-32.
 27. POLANO, O.: Quoted by Saenger, Hans.
 28. BRACK, W.: Über den Unterschied zwischen normalem und abnormen Ansprechen auf Ergotamin, Belladonna und Scopolamin, *Klin. Wchnschr.*, 1929, viii, 1652-1655.
 29. SCHÖNBAUER, L.: Zur Behandlung des Morbus Basedow mit Ergotamin (Gynergen), *Deutsch. Ztschr. f. Chir.*, 1926, cxviii, 99-100.
 30. PLATT, ROBERT: Über die Behandlung des Morbus Basedow mit Ergotamin, *Klin. Wchnschr.*, 1930, ix, 258-261.
 31. SPECK, WALTHER: Gefahr des Mutterkornbrandes bei Anwendung von Gynergen (Sandoz) in der Basedow-Chirurgie, *Med. Klin.*, 1930, ii, 1521-1523.
 32. ZORN, DIETRICH: Gynergenschädigung und ihre Beseitigung durch Wechselfussbäder und Padutin, *Deutsch. med. Wchnschr.*, 1931, ii, 1978-1979.
 33. MÜLLER, KONRAD: Zur Frage der Behandlung des Morbus Basedowii mit Ergotamin, *München. med. Wchnschr.*, 1933, ii, 1784-1786.
 34. YATER, W. M., and CAHILL, J. A.: Bilateral gangrene of feet due to ergotamine tartrate used for pruritus of jaundice: report of a case studied arteriographically and pathologically, *Jr. Am. Med. Assoc.*, 1936, cvi, 1625-1631.

35. GOULD, S. E., PRICE, A. E., and GINSBERG, H. I.: Gangrene and death following ergotamine tartrate (gynergen) therapy, *Jr. Am. Med. Assoc.*, 1936, cvi, 1631-1635.
36. PERLOW, SAMUEL, and BLOCH, LEON: Impending gangrene of the feet due to ergotamine tartrate: report of a case treated successfully, *Jr. Am. Med. Assoc.*, 1937, cix, 27-28.
37. LABBÉ, MARCEL, BOULIN, R., JUSTIN-BESANÇON and GUYEN: L'angine de poitrine ergotaminique, *Presse méd.*, 1929, ii, 1069.
38. ZIMMERMANN, OSKAR: Störung der Coronardurchblutung durch Ergotamin, *Klin. Wchenschr.*, 1935, xiv, 500-503.
39. PANTER, HERBERT: Tabische Symptome nach Gynergen-Injektionen, *Med. Klin.*, 1926, i, 880-881.
40. BABER, E. A., and TIETZ, ESTHER B.: The effect of ergotamine tartrate on the behavior of psychotic patients, *Jr. Med.*, 1937, xvii, 551-557.
41. GAYSINOVICH, S., KENIGSBERG, E., and KOGAN, A.: Symptoms and prophylaxis of ergotism, *Vrachebnoe Dielo, Kharkov.*, 1934, xvii, 433. *Abst., Jr. Am. Med. Assoc.*, 1935, civ, 167.
42. CAFFIER, P.: Streptokokkeninfektion und Sekalepräparate, *Zentralbl. f. Gynäk.*, 1928, lii, 1953-1965.
43. LEWIS, THOMAS, and GELFAND, B.: The manner in which necrosis arises in the fowl's comb under ergot poisoning, *Clin. Sci.*, 1935, ii, 43-55.
44. RUBIN, M. I., and RAPOPORT, MILTON: Effect of magnesium on vascular spasm in rats, *Arch. Int. Med.*, 1937, lix, 714-723.
45. HORTON, B. T., ROTH, GRACE M., and ADSON, A. W.: Observations on some differences in the vasomotor reactions of the hands and feet, *Proc. Staff Meet. Mayo Clinic*, 1936, xi, 433-437.
46. ALLEN, E. V., and MACLEAN, A. R.: Treatment of sudden arterial occlusion with papaverin hydrochloride: report of case, *Proc. Staff Meet. Mayo Clinic*, 1935, x, 216-220.

VITAMIN A CONTENT OF THE HUMAN LIVER IN TUBERCULOSIS *

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THE vitamin A content of human livers was determined photometrically in 50 patients in whom tuberculosis was the cause of death. The vitamin A content of their diet averaged from 5,000 to 8,000 U.S.P. units per day. All patients were fed the general hospital diet, except those with tuberculous enteritis. These were given a modified ulcer or soft diet of a similar vitamin A content. Six patients were given a supplemental dosage of vitamin A.

The findings were evaluated according to the average vitamin A content per gram of liver, age, supplemental dosage, duration and febrile course of manifest disease and the presence of tuberculous enteritis.

METHOD

The total liver weight was noted. To a 100-gram portion of finely ground liver, 500 c.c. of potassium hydroxide (5 per cent) were added. This mixture, after standing 48 hours, was heated to boiling for 30 minutes, cooled and extracted eight times with ether. The combined extracts were washed three times with distilled water, or until the washings were not alkaline to litmus. The extract was dehydrated with anhydrous sodium sulphate, filtered and evaporated to dryness under vacuum. The residue was weighed as unsaponifiable matter and spectrophotometric determinations made with a Hilger Vitameter.

RESULTS

The liver contents of vitamin A ranged from essential depletion (less than 3 U.S.P. units of vitamin A per gm.) to a maximum of 1640 units per gm. The average for the 50 cases was 342 units per gm. The average content according to age is given in table 1. The six patients who received a supplemental dosage of about 70,000 units of vitamin A per day, over periods of one to three months, averaged a vitamin A liver content of 628 units per gm., as compared with 313 units for the patients having no other source of vitamin A than the hospital diet. Included in this group is a patient who received 10,700,000 units of vitamin A over a period of 120 days. This individual came to autopsy three years later following a fulminating case of pulmonary tuberculosis of one year's duration. During the interim the patient was on the hospital high vitamin A diet. The spectrophotometric analysis revealed only 64 units of vitamin A per gm. of liver.

* Received for publication October 28, 1938.

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The vitamin A content per gram is essentially the same, regardless of the duration of the disease. Patients with a febrile course in excess of 100° F. reveal the vitamin A content of the liver reduced about 50 per cent, as compared with the cases having febrile courses below 100° F. The vitamin A content of the latter type of case compares favorably with the average found for normal persons. Hospitalization on the high vitamin A diet contributed to a moderate increase in the liver content of vitamin A. This increase was of about one-third, and was fully manifest within 100 days of hospital stay.

Intestinal tuberculosis was a clinical feature in 36 per cent and a gross pathological finding in 44 per cent of the cases. Patients with enteritis averaged 180 units of vitamin A per gm., as compared with 313 units for those with no evidence of this complication.

In this series, one patient manifested essential depletion of vitamin A as shown by the liver analysis. Seven patients averaged less than 30 units per gm. and 16 had less than 100 units per gm. of liver. Thus, half of all the patients had less than one-third of the vitamin A reported for normal persons. All patients with enteritis were below the average for the series, as well as the average for normal individuals.

DISCUSSION

The average liver content of all patients (342 units per gm.) compares favorably with that reported (331 units) in a previous paper¹ for healthy persons. The vitamin A liver content in the present group demonstrates that the average finding is far from the saturation point, as evidenced by the wide variation between it and individual cases. The average is about one-fifth of the maximum finding.

The distribution according to age is not significant, except for the fact that in older individuals the vitamin A content is somewhat increased (table 1). The abundant nutrition given phthisical patients and the prolonged duration of the fibrotic disease would account for these results.

From experimental work on dogs, the authors² estimated that approximately 1800 units of vitamin A were utilized daily by a normal, average human being. The hospital diet thus offers 3 to 4.5 times the average intake. The high vitamin diet of the tuberculosis hospital furnishes sufficient vitamin A for storage, whether it is absorbed or not. This might well explain the increased liver content of vitamin A in the cases of prolonged hospitalization, which is fully manifest within 100 days (table 1). The patients surviving less than 100 days, having either far advanced or fulminating disease, exhibit a more marked pyrexia and usually a terminal enteritis. The increased metabolic rate, due to the pyrexia and the enteritis, with faulty absorption, tends either to prevent or deplete the usual vitamin A supply of the body. Those surviving less than one year show but little

TABLE I
Vitamin A Content of Human Liver in Tuberculosis—50 Cases

	Number of Cases	U.S.P. Units per Gm. of Liver
AGE RANGE:		
15-20 years.....	4	684
20-30 years.....	18	276
30-40 years.....	8	226
40-50 years.....	11	219
50-60 years.....	6	430
60 and over.....	3	532
DURATION OF DISEASE:		
Less than one year.....	25	295
More than one year.....	25	285
PYREXIA:		
Below 100° F.....	26	423
Above 100° F.....	24	253
HOSPITAL DAYS:		
Less than 100 days.....	29	237
More than 100 days.....	21	358
Less than one year.....	38	352
More than one year.....	12	304
ENTERITIS:		
Absent.....	32	423
Present.....	18	180
AVERAGE	All Cases	341
Minimum.....	Less than 3 units per gm.	
Maximum.....	1640 units per gm.	

difference from those surviving 100 days. All patients with enteritis were below the average and many approached depletion.

SUMMARY

1. The average vitamin A content of human livers in 50 cases of tuberculosis was 342 U.S.P. units of vitamin A per gm. The minimum was practically depletion (3 units) and the maximum was 1640 units per gm. of liver.

2. The vitamin A content of the human liver approached depletion in 14 per cent of the patients.

3. Administration of generous doses of vitamin A is indicated in tuberculosis with pyrexia or enteritis.

REFERENCES

1. CRIMM, P. D., and SHORT, D. M.: Vitamin A content of human liver, *Am. Jr. Med. Sci.*, 1935, *clxxxix*, 571-573.
2. CRIMM, P. D., and SHORT, D. M.: Vitamin A deficiency in the dog, *Am. Jr. Physiol.*, 1937, *cxviii*, 477-482.

THE RÔLE OF SYMPTOMS AND SIGNS IN AMEBIASIS *

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THE belief prevails among many clinicians that symptoms and signs associated with amebiasis, particularly when subjective and objective deviations are not readily attributable to other factors, indicate that such changes are due to *Endameba histolytica*. The earlier parasitological viewpoint as expressed by Craig^{1,2} was not dissimilar. Our experience of more than a decade with clinical-parasitological problems denotes that this is not wholly true. The parasitological viewpoint in recent years has become similarly modified as evidenced in Craig and Faust's³ later writings. Thus, many carriers † of *E. histolytica* are in reality symptomless; in some others, the vaguer or more general symptoms and signs ordinarily attributable to this parasite when it is encountered, do not seem to be caused by it; not all diarrheas and dysenteries with which *E. histolytica* is associated can be said definitely to have been brought about by it. It is our impression, because of the type of inquiries often made of us by practitioners, that clinical knowledge in this connection lags behind the protozoölogical. Hence the presentation of the following data to emphasize the clinical problems involved, and the possible interpretation of symptoms and signs in relation to amebiasis.

CLINICAL DATA

GROUP I. Those with *E. histolytica* in the stools, without symptoms, with and without signs.

A. Those with Endameba histolytica without symptoms and signs. Six women, five white and one colored, and four men, three white and one colored, whose ages ranged from 16 to 26, were discovered during the course of examinations on defecated specimens of feces routinely performed upon successful applicants for hospital positions, to harbor *E. histolytica*. Upon this finding, they were reëxamined with a view toward ascertaining any symptoms and signs which might have borne some relationship to this infection. All data, including repeated history and physical examination, as well as blood count, blood Wassermann, urinary examinations, roentgenoscopic study of the chest and digestive apparatus, gastric analysis, as well as rectosigmoidoscopy, were completely negative.

* Received for publication October 10, 1938.

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† The expression "carriers of *E. histolytica*," as used in this paper, refers to individuals harboring *E. histolytica* which commonly appears in their stools as cysts, but who do *not* seem to be experiencing symptoms such as loose or frequent stools, intestinal bleeding, etc., presumably due to the presence of the parasite.

All were given carbarsone (Lilly, 4-carbamino-phenyl-arsonic acid: 28.8 per cent arsenic) 0.25 gm., twice daily for ten days. Seven were observed over six months, during which three specimens of saline-purged feces were examined monthly. The remainder were seen over a lesser time. In this group, the parasite was never encountered in any specimen subsequent to carbarsone administration. Subjectively and objectively, all were well before and after treatment.

B. Those with Endameba histolytica and without symptoms. A group of 10 food handlers—encountered during a protozoölogic survey—were discovered to have cysts of *E. histolytica* in defecated specimens of feces. It was only possible to ascertain that all had no symptoms; uncontrollable circumstances prevented objective study.

GROUP II. Those with *E. histolytica* in the stools with symptoms and signs.

A. Those without diarrhea and dysentery. Nine men, seven white and two colored, and six women, five white and one colored—a total of 15—whose ages ranged from 20 to 60, who came to the gastrointestinal section of the Johns Hopkins Hospital for relief from various and sundry abdominal complaints but who had no diarrhea or dysentery, were found to harbor *E. histolytica* in defecated specimens of feces. Submitted to the type of study already referred to, they were found to be free from demonstrable organic disease but some manifested changes in digestive tone or gastric secretion. It had been taught that there was an etiologic relationship between the presence of this parasite and such complaints. Indeed, this impression still prevails among many clinicians. It was hypothesized by us that if this were true, complete eradication of the parasite should result in elimination of complaints. Thereupon, each case was given 0.25 gm. carbarsone per os, twice daily for 10 days. They were observed over six months during which three specimens of saline-purged feces were examined monthly. With the exception of one case, the parasite was never encountered in any specimen subsequent to carbarsone administration. This exceptional instance responded eventually to a repeated course of carbarsone and one course of vioform (iodochloroxyquinoline). Suffice it to say that carbarsone gave relief from symptoms in the majority for a maximum of three weeks following its prescription. In all cases, long before the six month period had elapsed, and in the face of parasite eradication, similar symptoms had recurred with at least equal severity and prominence. These symptoms were then adequately controlled by antispasmodics, sedatives and hypnotics. Cessation of these measures resulted in undiminished recurring symptoms even in the continued absence of *E. histolytica*. Symptoms again subsided upon the reinstitution of this type of pharmacotherapy. Objectively, alterations in tone and secretion were not constant and did not parallel subjective relief.

There is no satisfactory explanation for the transient relief coincidental with carbarsone administration. This has been seen not infrequently—

during the course of this study—in cases with vague abdominal symptoms in which *E. histolytica* could never be demonstrated. Can it be ascribed to the tonic influence of arsenic? Can it be ascribed to psychotherapy? If the latter were completely true, one would have expected at least one case to be markedly benefited for six months—the duration of the observation period.

B. Those with diarrhea and dysentery. This communication is not concerned with those cases presenting symptoms among which are diarrhea or dysentery associated with *E. histolytica* in which there is complete relief from subjective and objective manifestations upon the eradication of the parasite. Such are cases of true amebic diarrhea, amebic dysentery, or amebic colitis. They are clearly understood and need no further comment.

Special attention is directed here to the type of case which has, among other complaints, dysentery or diarrhea but in which after eradication of the parasite, there is no complete cessation of the subjective and objective picture.

A case in point is as follows: A 19 year old white male, American born, entered the Johns Hopkins Hospital on November 22, 1933, with a history of three or four bloody, liquid bowel movements daily for the last two months. Objectively, *E. histolytica* and an ulcerative colitis were encountered. A diagnosis of amebic dysentery was made. He was given adequate courses of yatren, carbarsone, and emetine hydrochloride. The parasite was never encountered upon repeated examinations but his colitis persisted with little improvement as late as January 6, 1936, more than two years later. When last seen on April 2, 1937, the bowel was better but much muco-pus was still in evidence and the involved tissue was very friable.

Cases of this type, some with greater improvement, are infrequent but not rare; they have been referred to by Kiefer,⁴ Craig⁵ and Meleney and Frye.⁶ At present, it is not possible to say when the presence of *E. histolytica* is primarily, partly, or not at all responsible for symptoms and signs in such instances for the following reasons:

Five to 10 per cent of the population are said to be infected with *E. histolytica*, most of them healthy carriers. Is it not possible that one or more of these individuals may develop colitis on an entirely different basis? Unless there is some antagonism between amebic colonization and the non-amebic colitides, the theoretical expectation, based upon the amebic prevalence cited above, is that from 5 to 10 per cent of the persons with non-amebic colitis should harbor *E. histolytica* fortuitously. How, then, can this be differentiated from the type of colitis in which *E. histolytica* is the causative agent, and in the eradication of which "cure" does not result? Also, is it not possible to acquire the parasite subsequent to the initiation of a colitis non-amebic in origin? Clinical improvement (not complete relief) upon amebicidal therapy cannot be used to determine the rôle of *E. histolytica* under these circumstances. Non-specific ulcerative colitis sometimes responds similarly to amebicides: clinical improvement occurring without complete relief. Also, pharmacotherapeutic knowledge of amebicides in the

complete relief of amebic involvement, does not permit any definite deductions as to the significance of its effectiveness in part.

INTERPRETATIONS AND SUMMARY

1. A study was undertaken to evaluate the rôle of signs and symptoms in human amebiasis. Ten individuals were found to harbor *E. histolytica* and—as far as modern diagnostic methods were able to ascertain—were well subjectively and objectively before and after amebicidal therapy. In them, at the time of study, the presence of *E. histolytica* was not incompatible with good health.

2. Fifteen cases found to harbor *E. histolytica* presented digestive symptoms which heretofore had been ascribed to this protozoön. Eradication of the parasite did not eliminate symptoms and signs. The symptoms were controlled by antispasmodics, sedatives and hypnotics, and recurred—in the absence of this parasite—when these pharmacotherapeutic measures were withdrawn, and were again relieved by their re-administration.

3. Finally, the rôle of signs and symptoms in amebiasis is to be determined by the response to specific therapy. If there is complete, not partial, response, subjectively and objectively, upon amebicidal therapy coincidental with eradication of the parasite, then it may be said that there was a cause and effect relation between parasite and host manifestations. Our present knowledge does not permit the etiologic evaluation of *E. histolytica* in the production of signs and symptoms when the clinical responses to amebicides are partial in the face of parasitologic eradication. Thus, given a colitis or dysentery plus *E. histolytica*, it appears not to be possible to say that *E. histolytica* is the prime causative agent unless there is complete (not partial) subjective and objective response to specific therapy.

4. There is nothing in this communication which is to be construed as indicating that those harboring *E. histolytica* should not be treated. Parasite eradication should always be undertaken from the standpoint of prevention and as a public health measure.

REFERENCES

1. CRAIG, C. F.: Symptomatology, diagnosis and treatment of carriers of *Endameba histolytica*, Jr. Am. Med. Assoc., 1928, xc, 1345-1349.
2. CRAIG, C. F.: Amebiasis and amebic dysentery, 1934, Charles C. Thomas, Springfield, Illinois, 120-128.
3. CRAIG, C. F., and FAUST, E. C.: Clinical parasitology, 1937, Lea and Febiger, Philadelphia, 56-57.
4. KIEFER, E. D.: The Craig complement-fixation test for amebiasis in chronic ulcerative colitis, Am. Jr. Med. Sci., 1932, clxxxiii, 624-631.
5. CRAIG, C. F.: Further observations upon the complement fixation test in the diagnosis of amebiasis, Jr. Lab. and Clin. Med., 1933, xviii, 873-881.
6. MELENEY, H. E., and FRYE, W. W.: Practical value and significance of the complement fixation reaction in amebiasis, Am. Jr. Pub. Health, 1937, xxvii, 505-510.

INTERSEXUALITY OR PSEUDO-HERMAPHRODISM *

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It is generally assumed that the sex of an individual is determined at its inception by specific genetic factors, but in order for the genetically determined sex to be expressed anatomically, certain conditions must prevail during the developmental period. The sex-hormone complex which plays an important rôle in the development of sexual structures is normally in accord with the genetic factors so that development proceeds toward the expression of the genetically determined sex. However, alteration in the sex-hormone complex can result in modification of the normal course of sexual differentiation so that abnormal conditions may arise.

The anatomical expression of sex does not occur until relatively late in development. Up to this stage in development the embryo is in a sexually indifferent stage, i.e., every embryo, regardless of its future sex, has all the anlage necessary for development in either the male or the female direction. In normal male development the indifferent gonad differentiates into a testis, at the age of six or seven weeks. The Wolffian duct is stimulated and differentiates into its component parts, the epididymis, vas deferens, seminal vesicle and ejaculatory duct. The Müllerian duct, on the contrary, degenerates except for some nonfunctional remnants. The urogenital sinus and genital tubercle are stimulated to produce prostate glands, Cowper's glands, a male type of urethra, the scrotum and a penis. In normal female development the gonad differentiates into an ovary. The Müllerian ducts are stimulated to develop into oviducts, uterus, and upper vagina, while the Wolffian ducts degenerate. The urogenital sinus and genital tubercle develop in the female direction and the lower vagina, female urethra, Bartholin's glands and external female genitalia are formed (figure 1—normal development).

It is believed that the sex hormones are important in the normal process of sexual differentiation. Good evidence for the profound influence of sex hormones on sexual differentiation has been obtained in amphibia and birds. The earlier experiments involved gonad grafts and parabiosis (the fusion of two embryos so that their vascular systems are confluent). In later years, since the isolation of the various sex hormones in the crystalline form, the technic of hormonal injection into the incubating egg or the amphibian

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The crystalline sex hormones used in these experiments were furnished through the courtesy of Dr. Ernst Oppenheimer of Ciba Pharmaceutical Corporation.

Part of the expenses of this experimental work were defrayed by a grant from the Josiah Macy, Jr. Foundation.

embryo has been used.¹⁻⁷ In these experiments evidence was obtained that the male hormone caused sexual differentiation in the male direction and that

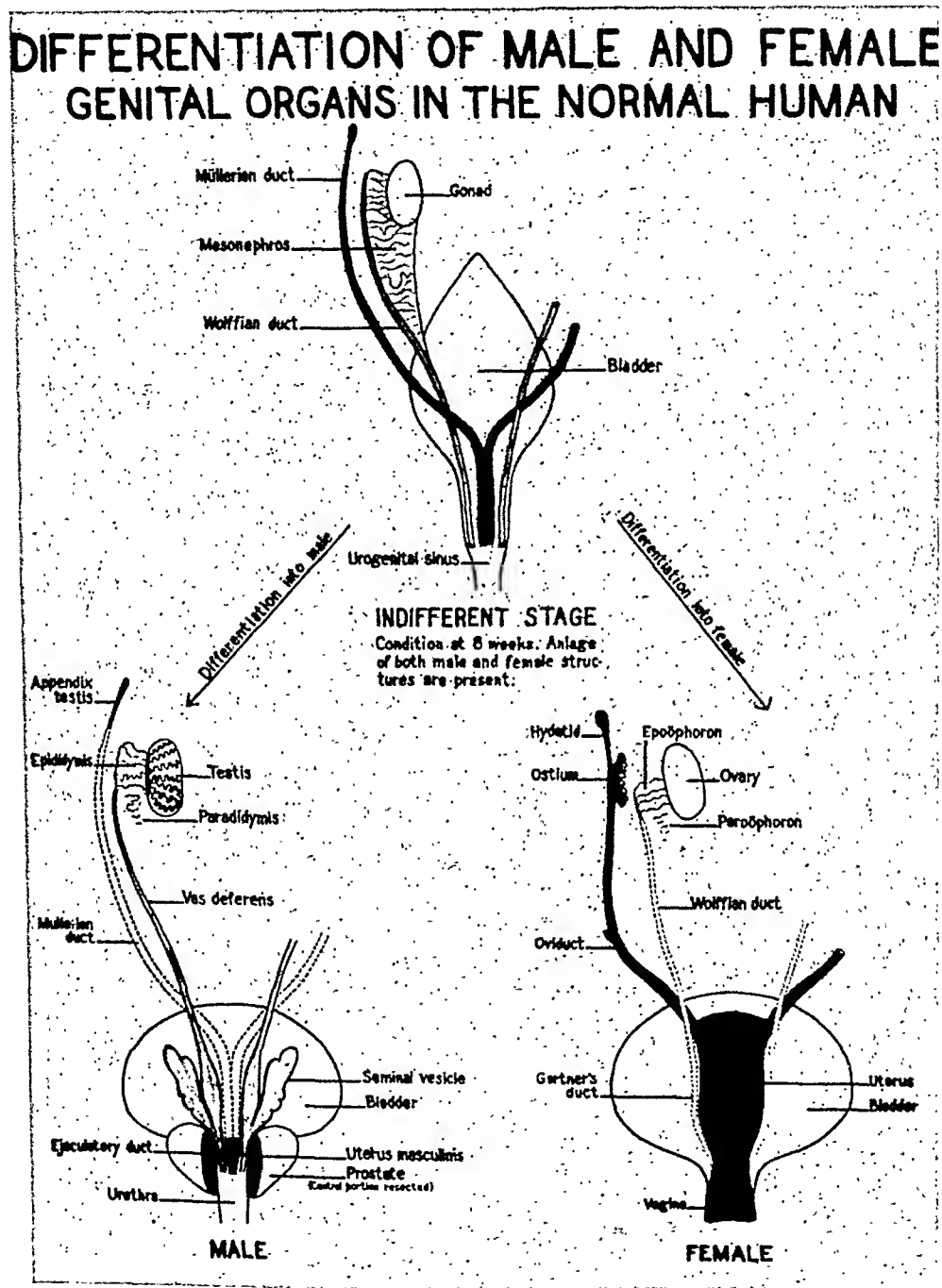


FIG. 1.

the female hormone caused differentiation in the opposite or female direction.

The mammalian embryo is not an isolated and self-sufficient unit as are

the embryos of the bird and amphibia. Therefore, until recently the mammalian embryo has been considered to be inaccessible for similar hormonal experimentation. However, in mammals, good evidence of the effect of the male hormone on embryonic sexual development has been obtained by study of the naturally occurring free-martin in cattle. Twins are not uncommon in cattle. Frequently, because of the diffuse nature of the placenta in these animals, vascular anastomoses occur between the twin placentae. When the twins are of the same sex, both are normal. When they are of opposite sex the male is normal, but the female is always masculinized. This masculinized female is the free-martin. The gonads of the free-martin are testicular-like in structure. The duct system is more or less completely masculinized while the external genitalia are usually feminine. Lillie,⁸ Keller and Tandler,⁹ and other workers have studied the free-martin extensively. Lillie has postulated that the alteration in the sexual development of the genetic female twin is caused by the male hormone produced in the male twin and transferred to the female through the vascular anastomosis. Two facts are known which make this postulate appear reasonable. First, the mammalian embryo, in its development, passes through an indifferent stage during which the anlage for both male and female structures coexist, and secondly, the male embryo undergoes sexual differentiation earlier than the female. Thus the male hormone which is produced in the male twin is transferred through the common blood stream to the female. The female is still undifferentiated so that the male hormone has a chance to mold the still plastic structures of the embryo in the male direction.

On the basis of evidence obtained from experiments on lower forms and from studies on the free-martin, it has been theorized that differentiation of the gonads is probably primarily under genetic control. The rest of sexual differentiation is, then, under control of the hormones produced by the gonads. That differentiation of the gonads is not influenced solely by genic factors has been shown by numerous workers inasmuch as partial or complete sex reversals—the production of testes instead of ovaries and vice versa—has been obtained in amphibia and birds by hormonal injections.¹⁻⁷

The *dihormonic theory*, or the theory that sexual differentiation in the male is influenced by male hormone, and in the female is influenced by female hormone has been widely accepted for the lower forms. Wiesner, however, has promulgated what he calls the *monhormonic theory* of sexual differentiation for mammals. He has postulated that only the male hormone plays a rôle in sexual differentiation. Sexual differentiation takes place in the female in the normal manner because no male hormone is present and female differentiation according to this theory is therefore anhormonic. Sexual differentiation takes place in the male in the normal manner because male hormone is present to cause such development. The female hormone has no influence on sexual development. The essential non-validity of this postulate will be demonstrated later.

Dantchakoff¹⁰⁻¹⁴ presented the first evidence that the male hormone is capable of masculinizing the embryonic mammal. She injected the male hormone directly into the amniotic cavity of 15-day embryonic guinea pigs and noted that a marked masculinization of the female embryos resulted.

Working without knowledge of Dantchakoff's discovery, we also obtained evidence that male hormones could markedly influence embryonic sexual development.¹⁵⁻¹⁷ Our method differed from Dantchakoff's in that the hormones were administered to the pregnant female. To date 256 pregnant rats have been injected with various androgens. Testosterone, which is presumably the true male hormone as found in the testes, was the first substance used. Other androgens used were: testosterone propionate, androsterone, dehydroandrosterone and androstenedione. One hundred eighteen of these injected pregnant rats have carried their pregnancies to term. The male offspring of these litters have been essentially normal, but the female offspring have been markedly masculinized. Two hundred fourteen intersexed or masculinized female rats have been obtained and examined either as newborn or as adults. Well modified animals resemble the male in that no external vagina is present and the phallus is a penis instead of a clitoris. Internally these animals have organs of both sexes. Oviducts, uteri and upper vagina are present combined with epididymides, ejaculatory ducts, the various prostatic lobes, a male urethra and Cowper's glands. The portion of the upper vagina which is present communicates with the urethra at the level of the normal uterus masculinis. No lower vagina is present.

Raynaud,^{18, 20} using our method, subsequently confirmed these findings in the mouse. A definite effect of the male hormone on sexual development has been demonstrated, then, in three different mammals, the guinea pig, the rat and the mouse.

In theory, a similar demonstration of the opposite effect, i.e., the effect of female sex hormone on sexual development, would be impossible. The administration of estrogenic substances to the pregnant animal has been claimed by various workers to interfere with pregnancy either by causing abortion or by causing fetal deaths and resorptions of the pregnancies. However, we have administered large doses of various estrogens to 212 pregnant rats. One hundred of these animals have carried their pregnancies to term. The estrogens which have been used are: estradiol, the probable true ovarian follicular hormone; and estradiol dipropionate, a doubly esterified form having a more prolonged effect than estradiol. As a result of this treatment, a marked feminization of the genetic male offspring has been obtained. One hundred and twenty-five of these intersexed or feminized male rats have been examined to date. Typically female structures, such as nipples, vagina and portions of the uteri and oviducts, are found. In addition, there is a marked inhibition in the development of male structures. Prostates are not present. Seminal vesicles are very small and may not be grossly visible in the adult. The vasa deferentia and epididymides are

partly or almost completely absent. The gonads are in a position typical for the female rat, i.e., at the base of the kidneys. The external genitalia are also feminized in that the phallus is small and hypospadiac with the vagina and urethra having a common opening at its base.

These experimental results show that the sexual development of the genetic female may be modified in the male direction by male sex hormone and that the sexual development of the genetic male may be modified in the female direction by female sex hormone. These results therefore lend credence to the dihormonic theory and apparently disprove Wiesner's postulated monhormonic theory inasmuch as the female hormone has been shown to have a profound effect on the sexual development of the genetic male.

The dihormonic theory is generally interpreted to mean that sexual development in the male is solely under the control of male hormone produced in the embryonic testes and that development of the female is solely under the control of female hormone produced in the embryonic ovaries. The male hormone, then, causes the Müllerian duct to degenerate and causes the Wolffian duct to develop into epididymis, vas deferens, etc., and the urogenital sinus to form prostates, etc. The female hormone causes the Wolffian duct to degenerate and causes the Müllerian duct to develop into oviducts, uteri and upper vagina and the urogenital sinus to develop into lower vagina and female urethra.

Further analysis shows that our experimental findings do not entirely fit into this theory. The estrogens produce effects in accordance with their postulated functions in that they cause inhibition of the Wolffian duct, stimulation of the Müllerian duct and influence the urogenital sinus to develop in the female direction. The androgens, however, do not fully cooperate with the theory inasmuch as they cause stimulation of the Wolffian duct and modification of the urogenital sinus in the male direction, but have never shown any definite evidence of inhibiting Müllerian duct development. In the masculinized females, oviducts, uteri and upper or Müllerian, vagina are present intact.

The fact that part of our experimental findings do not entirely fit the theory does not necessarily destroy its essential validity. Perhaps the male hormones we have used are not identical in action with the embryonic male hormone, or perhaps the matter is quantitative, i.e., the administered androgen does not reach the embryo at the proper stage of development in sufficient quantity to inhibit Müllerian duct development.

However, further study of our experimental material has led to some very disturbing and, at present, somewhat inexplicable findings. Twenty newborn genetic female offspring of mothers which received various dosages of estrogens have been serially sectioned. In 19 of these animals definite evidence of masculinization has been found. Wolffian duct derivatives, the vasa deferentia and ejaculatory ducts, have been found in various stages of preservation. In addition there is some inhibition of female structures.

The ovarian capsule, which is normally present in the female, is lacking, and development of the urogenital portion of the vagina is inhibited. Inspection of the gonad is required usually to distinguish between the genetic males and the genetic females (figures 2A and B).

EFFECTS OF ANDROGENS

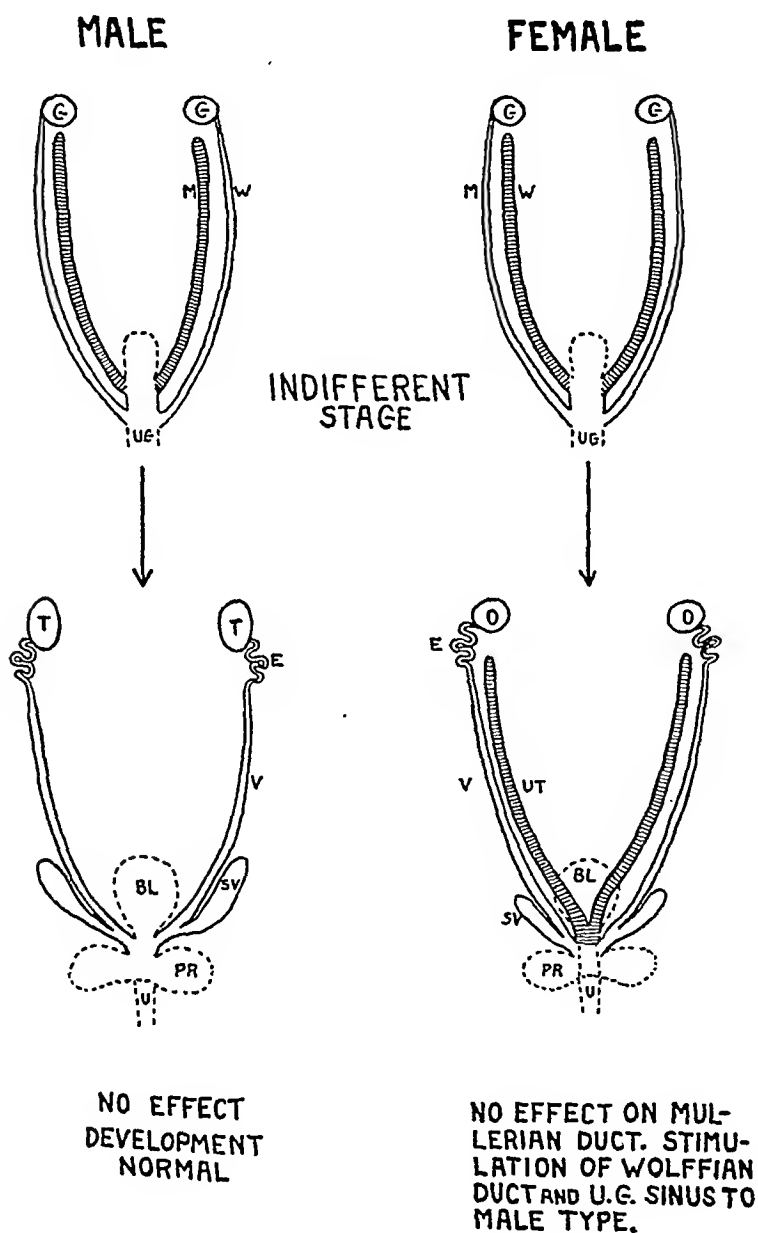


FIG. 2A.

Thus we have an apparent paradox. Administration of estrogens in large amounts to pregnant rats has caused "feminization" of the genetic male offspring and "masculinization" of the genetic female offspring.

It must be remembered, however, that these hormones have been administered to the pregnant rat. We are not justified in concluding that this masculinization of the female embryo is due to a *direct* action of the estrogen

EFFECTS OF ESTROGENS

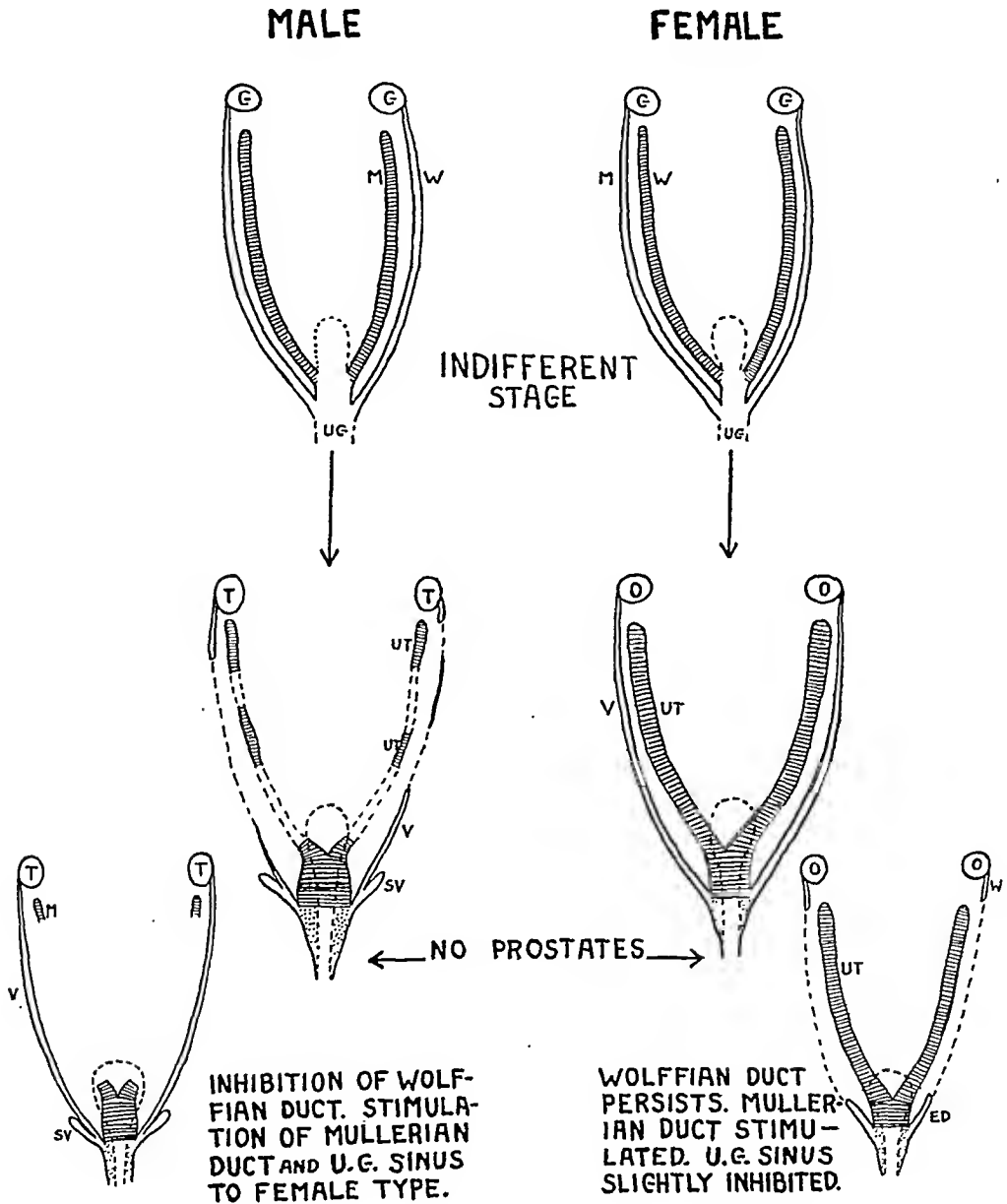


FIG. 2B.

on the embryo. The possibility that this effect is secondary in nature cannot be dismissed. It is well known that androgens are normally present in the female. Androgens have been extracted from ovaries,²¹ from adrenals²²

and from placentae,²³ but exactly where these androgens are produced is not known. Progesterone, the hormone of the normal corpus luteum, is also known to be androgenic.²⁴ Before it can be concluded that the estrogens administered to the pregnant rat have directly masculinized the female embryos in utero, a further possibility must be ruled out. The physiological mechanisms of the body are well balanced. In all probability the hormones of the pregnant organism (androgens plus estrogens) have little or no influence on the development of the embryo. When very large amounts of estrogens are introduced into the pregnant rat, perhaps the body, in an attempt to return the hormone balance to normal, causes a production of sufficient androgen to masculinize the female embryo. This explanation, however, is obviously inconsistent. If in response to administered estrogens, the pregnant rat produces sufficient androgen to masculinize the female embryo, one would expect the androgen so produced to counterbalance also the effects of the administered estrogens on the male embryo so that no feminization of the male should result.

In the case of the apparent paradoxical effects of estrogen, one has to consider the possibility that the relatively large doses suppressed the gonads either directly or indirectly via the anterior lobe. The entire matter is rather complicated and there is no immediate need to present an explanatory theory or hypothesis, which can be readily done. However, we shall await the accumulation of further experimental facts before exposing any new theory. It is sufficient for the present to state that the existing theories are in part inadequate and that sexual differentiation or development of a male or female mammalian embryo may be modified by the sex hormones.

CLINICAL APPLICATION

During the present century there have been numerous articles, monographs and books written about intersexuality in the human. Theories as to the mechanisms of production of these anomalies are almost as numerous as are the articles. No attempt will be made to review these articles or theories. However, an attempt will be made to explain some forms of human intersexuality on the basis of the knowledge gained from the study of experimentally produced intersexuality in mammals.

The occurrence of some forms of intersexuality in the human is much more common than is generally realized. Hugh Young has stated that pseudohermaphroditism occurs in one individual out of 1,000. It has been our privilege to observe three cases of pseudohermaphroditism in the human. Two of these cases were probably genetic females and one a genetic male. The findings in these individuals greatly resemble those in our experimental animals.

The two genetic females have previously been reported by Dr. H. O. Jones²⁵ and by Dr. W. T. Carlisle.²⁶ Both of these children externally resembled males in that a hypospadiac penis-like organ was present, while

no vagina was visible. Laparotomy revealed the presence of apparently normal ovaries, fallopian tubes, uterus and upper or Müllerian vagina. On cystoscopic examination (by Dr. Harry Culver) it was found that the vagina emptied into the urethra about 1 cm. below the bladder neck. Conditions identical with these have been found in some of our less well modified masculinized female rats obtained when androgen was administered late in the developmental period.

It is known that sexual differentiation of the external genitalia takes place relatively late in embryonic development. Apparently, in the female cases cited, an abnormal concentration of androgen affected development after the Wolffian ducts had already normally regressed but while the urogenital sinus and genital tubercle were still in a plastic stage so that they were influenced to develop in the male direction, consequently no lower

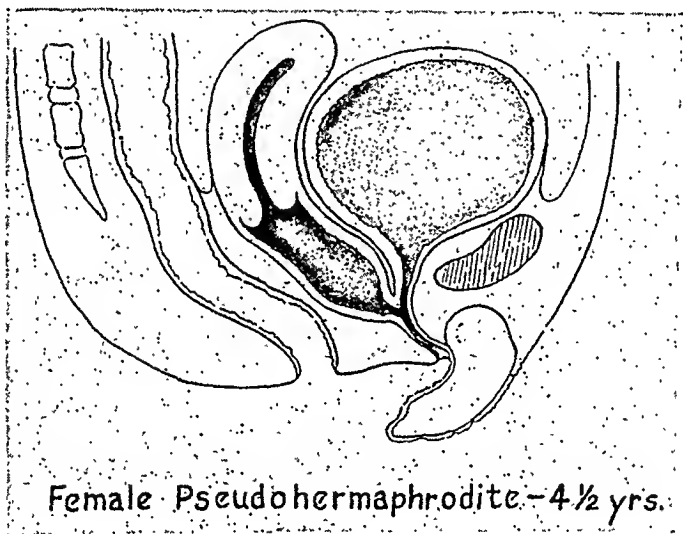


FIG. 3.

vagina is formed and a male type of phallus is developed. The upper or Müllerian vagina is left in communication with the urethra at the same level where, in the embryo, the Müllerian ducts communicate with the urogenital sinus (figure 3).

Externally the human male pseudohermaphrodite resembled a female, having a clitoris, large labia majora, labia minora, a vaginal introitus and female urethra. In the left labium majorum, however, a small testis with its epididymis was palpable. Another testis was palpable in the right groin. Laparotomy by Dr. Harry Culver revealed no evidence of a uterus nor of oviducts. This individual was 19 years old and had the habitus and hirsutes of a normal male.

In this individual an abnormal concentration of estrogen during embryonic development may have been the cause of the intersexed condition. An excessive amount of estrogen may have been present after degeneration of the Müllerian ducts had occurred, but before sexual differentia-

tion of the urogenital sinus and genital tubercle had taken place. These latter structures, being still in a plastic state, responded by developing in the female manner (figure 4).

Other cases presented in the literature may be explained in a similar manner. In some of these individuals hormonal influences apparently have been effective earlier in embryonic development and greater changes have resulted. Young²⁷ and Von Neugebauer²⁸ mention prostates in masculinized females. Young describes two cases of almost completely feminized males with testes, oviducts, uterus and vagina. Only one of these had any traces of Wolffian duct derivatives (vasa deferentia). In these individuals, if the conditions were hormonal in origin, abnormal concentrations of

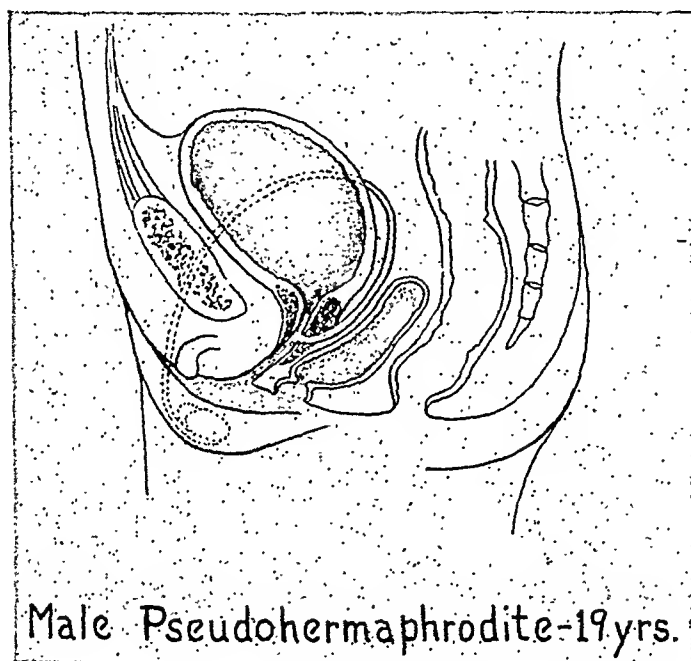


FIG. 4.

estrogens must have affected development in the very early plastic state, too late to influence differentiation of the gonads, but early enough to inhibit the Wolffian duct and stimulate the Müllerian duct and to cause female differentiation of the urogenital sinus.

We do not intend to imply that all cases of intersexuality in the human are due to hormonal conditions. It is quite probable that some of these abnormalities are directly due to genic factors. We also do not intend to enter into the discussion as to the sources of the hormones which may cause these abnormal sexual changes. Some may arise from abnormalities in the maternal organism. It has also been theorized that androgens produced by the abnormal fetal adrenals may be the causative agents in the production of masculinized female intersexes. In support of this theory is the fact that androgen producing adrenal hyperplasia or adenoma have been reported in masculinized females.

SEX BEHAVIOR

Since some psychiatrists believe that true sexual inversion, or homosexuality, is a congenital defect, many physicians have inquired about the sexual behavior of our intersexed rats. We can only say that our observations to date indicate that the definitely intersexed rats are "neutral" in that they respond neither as males nor as females. This neutral sexual behavior is like that of a gonadectomized rat some time after gonadectomy. This subject is one, however, in which the use of special technics or approaches is required to provide accurate data. We hope in the near future to make a scientific study of the problem.

It should be pointed out that the problem is capable of solution by scientific methods. The question is: Is true homosexuality a congenital defect that results from a sex hormone disturbance? The answer to that question depends on the answer to the following question: Does the male sex hormone prenatally or prepuberally organize in the brain a specific male behavior pattern? The same question, of course, applies to the female. We now know that the sexual activity of the castrated *mature male rat* is increased above the castration level by the daily injection of *female hormone*.²⁹ This shows that the male hormone does not specifically organize the male mating (copulatory and ejaculatory) behavior pattern in the adult male rat, but merely activates a pattern already present. The female hormone may arouse the male by causing congestion or tumescence of his genitalia. But, we do not know whether the adult male learned prior to castration to behave as a male, so that when estrogen was given him the tumescence of his genitalia caused him to act as formerly; or, whether his brain in utero or prepuberally was so organized by his own male hormone that he could behave only as a male? These and other questions must be answered before we can say whether homosexuality is congenitally acquired on the basis of a sex hormone disturbance. Of course, we know that sex hormones activate the sex urge, but we do not know that they specifically direct the urge in a male or female direction.³⁰ If it is found that sex hormones do not specifically organize sexual behavior in the rat, certainly they will not do so in man where environmental and psychological factors play such a prominent rôle. However, it must be remembered that a neuter-sexual person—a lack of both hormones or an anatomic pseudohermaphroditism—may be more readily directed in either the male or female direction of behavior by environmental conditions than a non-neuter-sexual person.

SUMMARY

Conclusive experimental evidence is now available showing that the sex hormones have a profound effect on the intrauterine sexual development in mammals.

REFERENCES

1. WILLIER, B. H., GALLAGHER, T. F., and KOCH, F. C.: Sex-modification in the chick embryo resulting from injections of male and female hormones, *Proc. Soc. Nat. Acad. Sci.*, 1935, xxi, 625.
2. WILLIER, B. H., GALLAGHER, T. F., and KOCH, F. C.: The modification of sex development in the chick embryo by male and female hormones, *Physiol. Zool.*, 1937, x, 101.
3. WILLIER, B. H.: The action of synthetic male hormones upon the differentiation of sex in the chick embryo, *Science*, 1937, lxxxvi, 409.
4. WOLFF, E.: Sur la réaction des canaux de Müller des Oiseaux aux hormones sexuelles, *Compt. rend. Soc. de biol.*, 1936, cxxiii, 237.
5. WOLFF, E.: Sur l'existence d'hormones intermédiaires susceptibles de masculiniser les femelles et de féminiser les mâles chez l'embryon de poulet, *Compt. rend. Soc. de biol.*, 1938, cxxviii, 420.
6. BURNS, R. K.: The effects of crystalline sex hormones on sex differentiation in amblystoma, *Anat. Rec.*, 1938, lxxi, 447.
7. GALLIEN, L.: Action des hormones sexuelles dans la différenciation du sexe chez *Rana temporaria* L, *Bull. Biol. France et Belg.*, 1938, lxxii, 269.
8. LILLIE, F. R.: The free-martin: A study of the action of sex hormones in the foetal life of cattle, *Jr. Exper. Zool.*, 1917, xxiii, 371.
9. KELLER, K., and TANDLER, J.: Über des Verhalten der Eihäute bei der Zwillings-Strächtigkeit des Rindes. Untersuchungen über die Entstehungsursache der geschlechtlichen Unterentwicklung von weiblichen Zwillings Kälbern, welche neben einem männlichen Kalbe zur Entwicklung gelangen, *Wien. tierärztl. Wchnschr.*, 1916, iii, 513.
10. DANTCHAKOFF, V.: L'hormone mâle adulte dans l'histogénès sexuelle du mammifère, *Compt. rend. Soc. de biol.*, 1936, cxxiii, 873.
11. DANTCHAKOFF, V.: Sur les faits acquis dans le domaine de la sexualité (avec démonstration), *Compt. rend. Soc. de biol.*, 1936, cxxii, 1307.
12. DANTCHAKOFF, V.: Sur l'édification des glandes annexes du tractus génital dans les free-martins et sur les facteurs formatifs dans l'histogénèse sexuelle mâle, *Compt. rend. Soc. de biol.*, 1937, cxxiv, 407.
13. DANTCHAKOFF, V.: Sur la faculté des tissus induits par l'hormone male d'édifier de nouvelles structures chez l'embryon de cobaye femelle, *Compt. rend. Soc. de biol.*, 1937, cxxiv, 516.
14. DANTCHAKOFF, V.: L'hormone mâle à la base de l'édification du pénis et de ses malformations chez les mammifères, *Compt.-rend. Soc. de biol.*, 1938, cxxvii, 674.
15. GREENE, R. R., and IVY, A. C.: The experimental production of intersexuality in the female rat with testosterone, *Science*, 1937, lxxxvi, 200.
16. GREENE, R. R., BURRILL, M. W., and IVY, A. C.: Further effects of androgenic substances on sexual development in the female white rat, *Proc. Soc. Exper. Biol. and Med.*, 1938, xxxviii, 1.
17. GREENE, R. R., BURRILL, M. W., and IVY, A. C.: Experimental intersexuality: The production of feminized male rats by antenatal treatment with estrogens, *Science*, 1938, lxxxviii, 130.
18. RAYNAUD, A.: Modifications apportées précocement dans la structure de la vessie et de l'urètre du chat par des injections de dihydrofolliculine, *Compt. rend. Soc. de biol.*, 1937, cxxvi, 215.
19. RAYNAUD, A.: Formation d'un urètre mâle, d'un pénis et absence de vagin chez les souris femelles intersexuées, *Compt. rend. Soc. de biol.*, 1938, cxxvii, 503.
20. RAYNAUD, A.: Intersexualité obtenue expérimentalement chez la souris femelle par action hormonale, *Bull. Biol.*, 1938, lxxii, 297.
21. PARKES, A. S.: Androgenic activity of ovarian extracts, *Nature*, 1937, cxxxix, 965.
22. REICHSTEIN, T.: Constituents of the adrenal cortex. II. Andrenosterone, *Helv. Chem. Acta.*, 1936, xix, 223.

23. GOECKE, W. D.: Amount of male sex hormone in placenta and urine in pregnancy and puerperium, *Arch. f. Gynäk.*, 1936, clxi, 295.
24. GREENE, R. R., BURRILL, M. W., and IVY, A. C.: Progesterone is androgenic, *Endocrinology*, 1939, xxiv, 351.
25. JONES, H. O.: Pseudohermaphroditism, *Am. Jr. Obst. and Gynec.*, 1938, xxxv, 701.
26. CARLISLE, W. T., and GEIGER, C. J.: Two cases of intersexuality, *Am. Jr. Obst. and Gynec.*, 1938, xxxvi, 1047.
27. YOUNG, HUGH: Human genital abnormalities, hermaphroditisms, and related adrenal disease, 1937, Williams and Wilkins, Baltimore.
28. VON NEUGEBAUER: Hermaphroditismus beim Menschen, 1908, W. Klinkhardt, Leipzig.
29. BALL, J.: Sex activity of castrated male rats increased by estrin administration, *Psychological Rev.*, 1938, xlv, 445.
30. LASHLEY, K. S.: Exp. analysis of instinctive behavior, *Psychological Rev.*, 1938, xlv, 445.

OBESITY AND HYPERTENSION: CLINICAL AND EXPERIMENTAL OBSERVATIONS *

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CLINICAL studies have indicated a definite correlation between obesity and increased systolic blood pressure. This observation has received statistical support from several angles. There is also a general impression among physicians that overweight unfavorably influences an existing essential hypertension, while often but not always blood pressure levels fall with weight reduction. Aside from these generalizations little can be learned from the literature relative to any specific or prolonged effects of weight reduction on hypertension. True enough, several small recorded series indicate blood pressure fall with weight reduction but we have found no long time experiments to indicate the contrary side of the question; namely, the effect of a rapid weight gain on blood pressure. Consequently we have attempted to study hypertensive and non-hypertensive dogs whose weight could be varied by the amount and kind of food intake. It is, therefore, the primary purpose of this paper to state briefly the effect of obesity on the systolic and diastolic pressures of dogs and, if possible, to draw any clinical application that might arise—an interesting but often misleading pastime.

Before going into the experimental side of the problem it seems advisable to note that a fairly strong correlation can be built up between obesity and hypertension along three general lines: First, statistical studies have been made on several large series of individuals who in the main can be considered normal. For example, in over 500,000 insured men¹ there was a definite rise of both systolic and diastolic pressure with increasing weight. Fortunately, in this study the age factor was carefully considered, and increasing weight still held as a definite correlation with rising blood pressure for all age groups. From a study of 5,364 white prisoners, Alvarez and Stanley² have concluded that after the age of 35 fatness tends to increase systolic blood pressure and thinness tends to decrease it. Fatness and leanness have a slight effect on diastolic pressure. Huber³ finds only slight statistical significance to a direct correlation between increased weight and increased systolic blood pressure in a study of 1,332 healthy men. Dunham⁴ likewise relates overweight and blood pressure elevation but indicates a closer association between variation in blood pressure and age than between variation in blood pressure and body weight.

A second and somewhat more exciting approach has been the clinical study of obesity and hypertension. Master and Oppenheimer⁵ reduced 53 obese patients with essential hypertension an average of 25 to 30 pounds

* Received for publication April 26, 1938.

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and observed an average fall of 25 to 30 mm. Hg in systolic blood pressure and 15 to 20 mm. Hg fall in the diastolic. It is not clear how long the pressure stayed down or its eventual course.

Symonds,⁶ in an analysis of 150,419 policy holders in the Mutual Life Insurance Company, found that systolic and diastolic blood pressure increased with both age and weight. These individuals were divided into 10 groups, four of which varied from 5 to 35 per cent below normal weight; a normal group, including those from 5 per cent below to 5 per cent above ideal weight; and five groups weighing from 5 per cent to 50 per cent more than normal. The blood pressures of these ten weight groups were tabulated according to age at intervals of five years from 15 to 60 years of age and over. Though there appeared a constant rise in blood pressure with both increasing age and weight the differences were small, the average blood pressure at age 40 to 44, for example, being 119 mm. Hg systolic and 79 diastolic for the group 35 per cent underweight; 126/83 mm. Hg for the normal group; and 133/89 mm. Hg for those who were 50 per cent overweight.

Dublin, Fiske, and Kopf⁷ in reviewing the results of periodic health examinations in 16,662 policy holders of the Metropolitan Life Insurance Company, found 20 per cent of these individuals to be overweight. Among this group 12.8 per cent showed elevations of blood pressure from 20 to 40 mm. Hg above normal. Only 2.5 per cent of the remaining number showed equally high blood pressure. These authors conclude that obesity and elevated blood pressure are very closely related.

Perhaps more closely approaching the question of relationship of pathological changes in blood pressure and body weight are the studies of consecutive patients admitted to hospitals and clinics, such as those of Hartman and Ghrist⁸ who studied the relationship of body weight to blood pressure in 2,042 consecutive registrants at the Mayo Clinic. In six groups of patients, varying from 50 per cent underweight to 75 per cent overweight, there was found to exist an almost step-like increase of systolic blood pressure from groups one to six. The diastolic pressure did not show such consistent changes. Therefore, weight was thought to be a dominant factor in determining systolic blood pressure.

Palmer⁹ finds obesity three times as often in 100 unselected cases of hypertension as in 100 unselected ward patients suffering from miscellaneous diseases.

The common occurrence of a fall in blood pressure in obese patients with hypertension who voluntarily lose an appreciable amount of weight is a well known fact. Bearing directly upon this question are the striking observations of Terry,¹⁰ made upon 63 obese female patients who showed an average blood pressure of 173/96 mm. Hg. The average weight of the individuals in this group was 199½ lbs. Though none of them showed any clinical symptoms of renal damage, 58 per cent were found to have definite hypertension. The average blood pressure of 24 members of this latter

group who were studied while on a reducing diet fell from 196/103 mm. Hg to 170/95 mm. Hg. The greatest loss of weight was 60 pounds in a period of 14 months. In this instance the blood pressure changed from 190/90 mm. Hg to 148/95 mm. Hg.

Still a third approach is somewhat more indirect but may have bearing on the subject. Randall¹⁰ noted the average gain in weight for primigravid women and found this to be 33 pounds for those who became victims of the late hypertensive toxemia of pregnancy, whereas the non-toxemic patients gained 22 pounds. From the records of the University of Virginia Hospital it appears that following the late hypertensive toxemia of pregnancy obese women are nine times as likely to develop residual hypertension as those who remain normal or near normal weight.

In brief, although a correlation apparently exists between overweight and elevated systolic pressure it cannot be said that obesity is a cause of essential hypertension. Many obese people have low blood pressure, whereas many thin persons have hypertension. However, if this association of overweight and hypertension does exist, obesity should be studied as a secondary factor sometimes precipitating a pressor mechanism.

For the past five years we have been making observations of the blood pressure of both normal dogs and dogs with experimentally produced hypertension. Lasting elevation of both systolic and diastolic pressure has been produced in these animals by three different methods: namely, excision of renal tissue, ligation of renal arteries, and partial obstruction to blood flow through the kidneys by application of Goldblatt clamps¹¹ to the renal arteries. The latter method has generally resulted in higher elevation of blood pressure for a longer period of time than have the other two procedures.

The blood pressure has been recorded by the method first introduced for unanesthetized dogs by Kolls,^{12, 13} in which the Erlanger¹⁴ method of recording human systolic and diastolic blood pressure has been adapted to this use. For a detailed description of this apparatus and method the reader is referred to a recent paper by the present authors¹⁵ in which a diagram appears indicating the several minor but advantageous changes in setting up the apparatus.

Our animals have been fed upon several brands of prepared dog food, each containing less than 20 per cent protein, to which have been added cod liver and raw beef at frequent intervals. Almost all of them have remained well nourished and otherwise apparently in healthy condition though, due to lack of space for out-door runways, it has been necessary for the dogs to remain in cages throughout the experiment. Thus, though far from a natural environment, their living conditions have been pretty well standardized.

Our present study began as the result of observations made upon one of the dogs of this group (figure 1; Dog C-34) to whose renal arteries Goldblatt clamps had been applied five months previously. This dog, whose

weight had fallen from 44 to 33.5 pounds, regained this loss within one month when fed three pounds of raw beef daily and, for the following three weeks, continued to gain weight on his regular diet without the beef. During this period both systolic and diastolic blood pressure, which had remained elevated throughout the period of poor nutrition, rose sharply to even greater heights but gradually fell to average post-operative levels when the

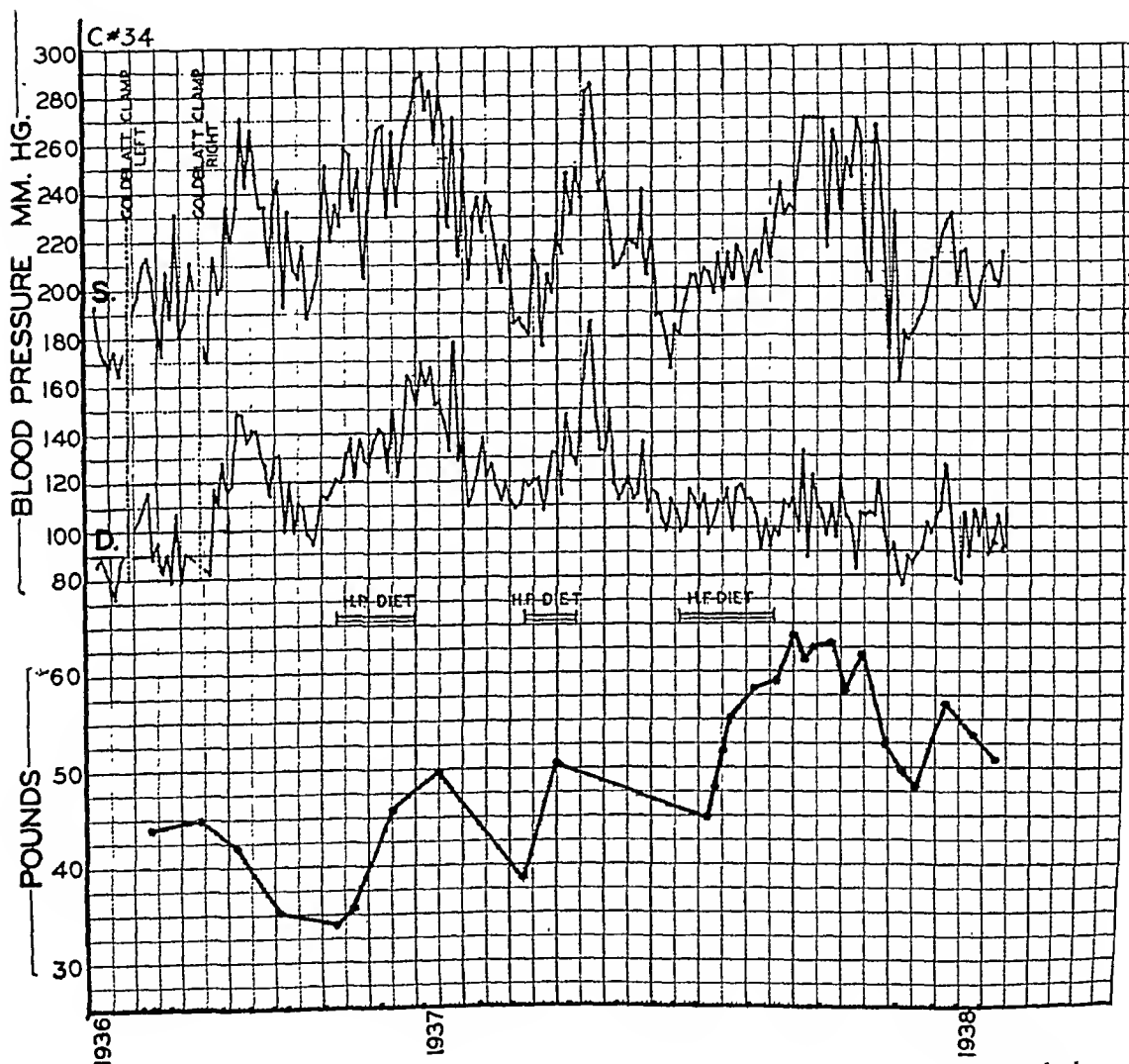


FIG. 1. Dog C No. 34: Mean systolic and diastolic blood pressure as related to body weight during all lean meat (H. P.) diet and standard plus high fat (H. F.) diet. Dog fed on standard diet during unmarked period.

meat was withdrawn from the diet. After an interval of two months, during which time the dog received the regular diet and lost approximately 9.5 pounds in weight, the blood pressure remained within the elevated range usually seen after constriction of the renal arteries. At this point the all meat diet was resumed. The prompt gain in weight of 12 pounds which followed was again accompanied by marked rises of both systolic and diastolic pressure.

During the course of this experiment two other dogs were placed upon a less abundant, all meat diet. One of these dogs had bilateral Goldblatt clamps, the other partial nephrectomy. These animals were well nourished at the beginning of the experiment and were given only one and one-fourth pounds of lean beef daily, an amount thought to be adequate for the maintenance of body weight but not sufficient to cause much gain. This was done for the purpose of determining whether or not an all meat diet would cause a rise in blood pressure in dogs who did not gain weight. The weight of neither animal changed materially during this time, nor did there occur any appreciable changes in blood pressure.

The result of this experiment suggested strongly that the increase in weight rather than the all meat diet was the factor more closely associated with the rise in blood pressure observed in Dog C-34 (figure 1). It then seemed desirable to us, before pursuing further the complicated question of the effect of proteins upon blood pressure to ascertain whether such rises in blood pressure followed increase of body weight produced by other types of diet. Accordingly, four normal dogs and four dogs with longstanding experimental hypertension were fed for one month mainly upon beef fat (table 1). Each of these animals received daily one pound of ground beef fat mixed with about a half pound of the usual standard dog food. Dogs quickly regurgitate large amounts of fat eaten alone but retain and ap-

TABLE I

BLOOD PRESSURE CHANGES RELATED TO CHANGE IN BODY WEIGHT IN EIGHT DOGS															
DOG	WEIGHT			BLOOD PRESSURE						WT.	B.P.		WT.	B.P.	
#	LEAN	FAT	LEAN	LEAN		FAT		LEAN		GAIN (LBS)	CHANGE		LOSS (LBS)	CHANGE	
				S.	D.	S.	D.	S.	D.		S.	D.			
31	39	50	41	216	106	252	98	171	85	11	+36	-8	9	-81	-13
34	45	63	49	196	106	245	109	177	85	18	+49	+3	14	-68	-24
3	33	44	36	176	92	214	85	169	83	11	+38	-7	8	-45	-2
2	28	33	28	153	84	156	79	153	81	5	+3	-5	5	-3	+2
33	35	51	44	123	67	172	68	131	57	16	+49	+1	7	-41	-11
16	31	36	31	166	78	224	84	179	65	5	+53	+6	5	-46	-19
35	35	51	43	158	82	185	83	168	82	16	+27	+1	8	-17	-1
30	30	41	31	152	69	167	71	132	54	11	+15	+2	10	-35	-17

Mean systolic and diastolic blood pressure before, during, and after weight gain for each dog. Dogs C No. 34 and C No. 31, hypertension produced by Goldblatt clamps. Dogs C No. 3 and C No. 2 hypertension produced by reduction of kidney tissue. Dogs C No. 33, C No. 16, C No. 35 and C No. 30 not subjected to any operative procedure; apparently normal dogs.

parently relish the mixture which these animals were given. After receiving this diet for a month, the dogs were again given their regular food in amounts varying from one-half to one pound daily, an attempt being made to regulate the food of each animal in such a manner that the weight would slowly decrease. It will be seen that we had considerable difficulty in accomplishing this end in several animals.

The results of this experiment are recorded in table 1. Dog C-2 (figure 2), whose right renal artery and two of three main branches of the left renal

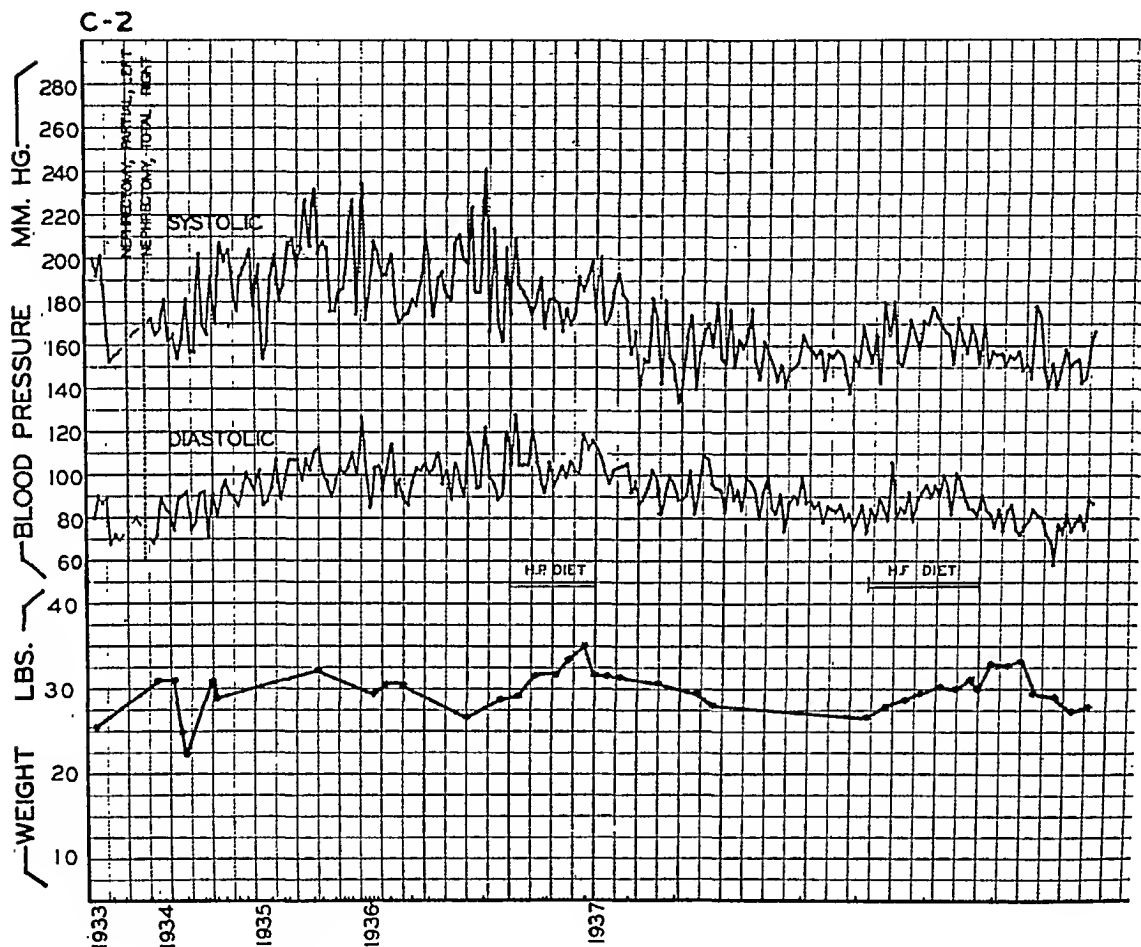


FIG. 2. Dog C No. 2: H. P. = High Protein Diet. H. F. = High Fat Diet.

artery were ligated in December 1933, has never varied much in weight during four years of observation. This animal did not gain appreciably on the high fat diet nor was there any significant change in either systolic or diastolic blood pressure during this period. All of the other seven dogs were well nourished at the beginning of the experiment and quite obese at the end. Each of them showed a marked rise of systolic blood pressure, often exceeding 280 mm. Hg, the highest pressure which we can record consistently with our apparatus. As the weights of the dogs decreased, systolic blood pressure returned to its original level in each case. No ap-

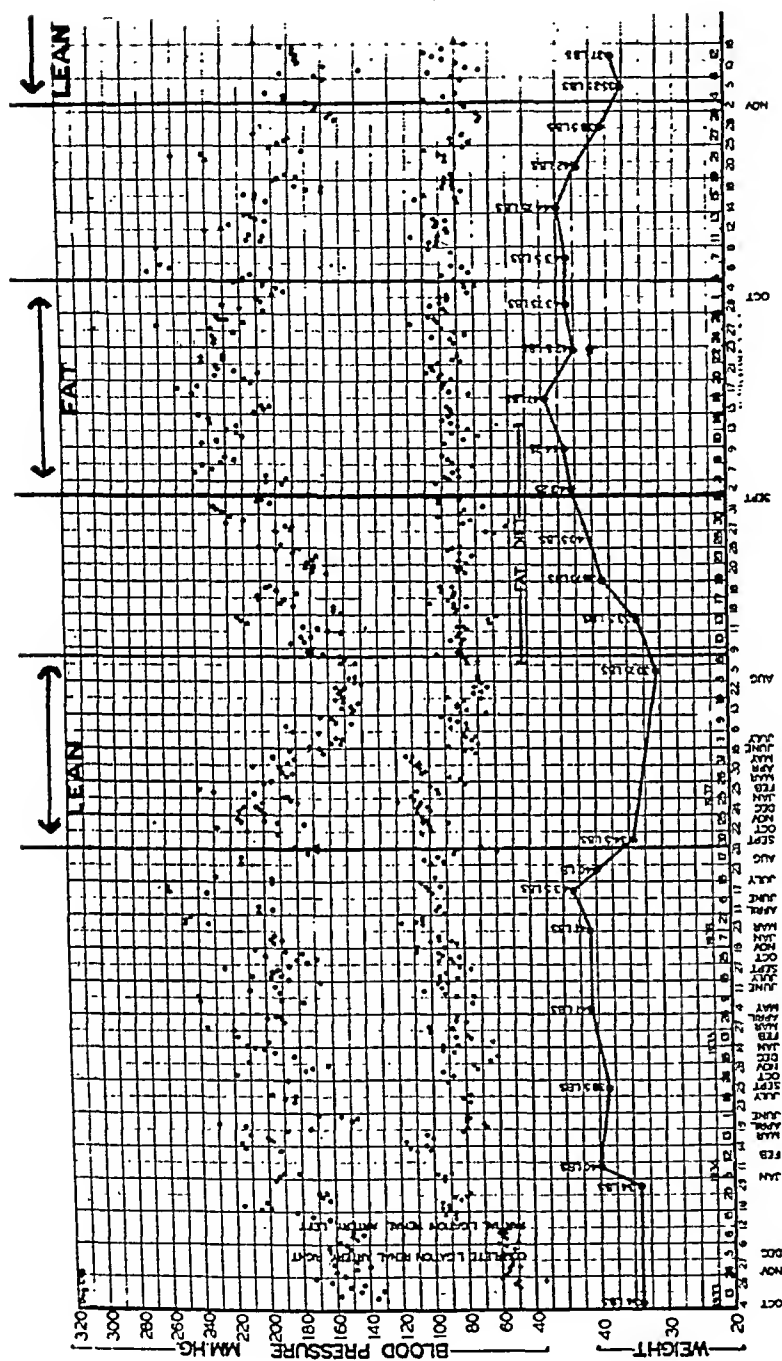


Fig. 3. Dog C No. 3: Individual systolic and diastolic blood pressures recorded in this dog to indicate method by which the mean figures before, during and after weight rise were obtained for table 1.

preciable rise of diastolic blood pressure occurred in any of these animals throughout the experiment, but an appreciable fall in diastolic pressure occurred in five of the eight animals following a sharp loss of weight.

Table 1 presents a summary of the effects of weight change in four hypertensive and four non-hypertensive dogs. In each instance the mean systolic and diastolic pressure has been determined over a period of a month or more prior to, during maximum weight gain, and after the animal has been reduced by food restriction to approximately the original weight level. In every instance except one a sharp rise of 15 to 53 mm. Hg systolic blood pressure occurred with a definite increase in weight. The one exception serves as an additional control observation. This animal (Dog C-2; figure 2), a large bony german shepherd, gained only five pounds, an insignificant weight gain for original size, and no change occurred in blood pressure level. Dog C-16, a small nervous mixed breed female, was quite well nourished at 31 pounds and a weight gain of five pounds made this animal quite fat with a sharp rise in systolic pressure. Equally as striking is the systolic pressure fall with weight loss. This frequently proved to be greater than the original rise. Little diastolic change occurred with the weight rise but with weight reduction diastolic pressure fell below its pre-diet level in five of the eight animals. It is not clear at present whether this recorded fact is of significance. These mean figures may be verified and studied in detail from the records of a previous publication.¹⁶

There is one criticism concerning the accuracy of the systolic blood pressure recorded in these experiments which we wish to mention at this time. It has been the common experience of all workers employing the apparatus which we have used that the cuff must be well fitted and placed as high as possible on the thigh to assure obliteration of the femoral artery. The possibility therefore exists that the increase in size of the leg which accompanies marked gain in weight might interfere to some extent with the compression of the underlying artery, thereby causing the systolic pressure only to appear to be elevated. It is possible that an error of from 5 to 10 mm. Hg might be due to this, but we do not think that such marked and consistent apparent elevations of systolic pressure could be accounted for in this manner. Our main basis for this belief is the consistency with which the systolic pressure rose apparently independently of the actual amount of weight gained.

In these experiments we have been careful to throw out all sphygmographic records in which systolic pressure was doubtful. That observations are accurate at widely separated weight levels is shown by the recorded curves on Dog C-34 where the systolic as well as diastolic pressure at 45 to 50 pounds is even higher than the pressure for 62 to 64 pounds weight. Again, in animal C-30 there is a sharp rise in weight, twelve pounds, with only a slight or moderate rise in systolic pressure. Previously published curves¹⁶ illustrating this method have suitably demonstrated wide variations in blood pressure at constant weights. Furthermore, maximum-minimum

valve studies to check the accuracy of the method have been reported.¹³ However, owing to the violent changes in weight the systolic observations should be checked by another method to establish the rather striking results reported here.

DISCUSSION

From these experiments it seems clear that both normal dogs and dogs with experimental hypertension produced by two different methods show marked increase of systolic blood pressure when caused to gain large amounts of weight by feeding them a diet composed chiefly of beef fat. Though the final explanation of this rise in blood pressure is not known, it seems most likely that it is intimately associated with the increase of body weight. This assumption is further supported by the fact that two dogs, whose weight was maintained by feeding raw beef only, showed no change in blood pressure, while one dog, fed entirely on raw beef in amount sufficient to cause marked gain in weight, developed marked elevation of both systolic and diastolic pressure. Though it is of considerable added interest that the diastolic pressure of this latter animal showed such a marked rise during the period of excessively abundant high protein diet, our studies of the experimental conditions to which this dog was subjected are not yet adequate to justify further comment.

It has been of much interest to us that both groups of dogs, hypertensive and normal, gaining weight on a high fat diet have shown a rise of systolic pressure only. This observation suggests that the hypertension of obesity is in some way fundamentally different from the hypertension experimentally produced by interference with blood flow through the kidneys, under which condition the diastolic as well as the systolic pressure is always elevated.

Weight reduction in patients has been followed by a fall in blood pressure and symptomatic improvement. Although this particular phase of the discussion does not fall within the scope of this paper we are not unmindful of the fact that improvement following weight reduction is not based on systolic blood pressure fall wholly, but mainly upon mechanical and chemical factors, particularly a reduction of cardiac work for exercise.¹⁷

This similarity in behavior of systolic blood pressure relative to body weight in dog and man does not imply a causal relationship between obesity and essential vascular hypertension. Furthermore, the rapidity of forced weight gain and weight loss in these dogs partially invalidates any careful comparison with clinical experience. The true relationship of obesity to human hypertension remains to be shown, but an explanation previously suggested,¹⁸ that obesity may act mechanically to produce increased resistance in the peripheral vascular stream bed, seems most likely.

CONCLUSIONS

The literature indicates a definite association between obesity and systolic blood pressure elevation in a fair number of instances.

Systolic blood pressure in normal and hypertensive dogs rises with weight gain and falls with weight loss, while diastolic pressure varies little.

These observations do not indicate that obesity is a cause of essential hypertension but support the idea that overweight may be a factor of importance in the elevation of systolic blood pressure.

REFERENCES

1. DUBLIN, L. I.: Personal communication based on report of Joint Committee on Mortality of the Association of Life Insurance Medical Directors and the Actuarial Society of America. Tables 7 and 8 (1925).
2. ALVAREZ, W. C., and STANLEY, L. L.: Blood pressure in six thousand prisoners and four hundred prison guards—a statistical analysis, *Arch. Int. Med.*, 1930, xlii, 17.
3. HUBER, E. G.: Systolic blood pressure of healthy adults in relation to body weight, *Jr. Am. Med. Assoc.*, 1937, lxxxviii, 1554.
4. DUNHAM, G. C.: Variation in blood pressure as associated with age and body weight, *Internat. Clinics, Series 35*, 1925, iii, 81.
5. MASTER, A. M., and OPPENHEIMER, E. T.: A study of obesity, *Jr. Am. Med. Assoc.*, 1929, xcii, 1653.
6. SYMONDS, B.: Blood pressure of healthy men and women, *Jr. Am. Med. Assoc.*, 1923, viii, 232.
7. DUBLIN, L. I., FISKE, E. L., and KOPF, E. W.: Physical defects as revealed by periodic health examinations, *Am. Jr. Med. Sci.*, 1925, clxx, 576.
8. HARTMAN, H. R., and GHRIST, D. H.: Blood pressure and weight, *Arch. Int. Med.*, 1929, cliv, 877.
9. PALMER, R. S.: Etiologic factors in hypertension, *New Eng. Jr. Med.*, 1931, ccv, 1233.
10. RANDALL, L. M.: The weight factor in pregnancy, *Am. Jr. Obst. and Gynec.*, 1925, ix, 529.
11. GOLDBLATT, H., LYNCH, J., HANSAL, R. F., and SUMMERVILLE, W. W.: Studies on experimental hypertension. I. The production of persistent elevation of systolic blood pressure by means of renal ischemia, *Jr. Exper. Med.*, 1934, lix, 347.
12. KOLLS, A. C.: An indirect method for the determination of blood pressure in the unanesthetized dog, *Jr. Pharmacol. and Exper. Therap.*, 1920, xv, 443.
13. KOLLS, A. C., and CASH, J. R.: The blood pressures in the unanesthetized dog, *Bull. Johns Hopkins Hosp.*, 1923, xxxiv, 49.
14. ERLANGER, J., and MEEK, W. J.: An adjustable sphygmoscope for the recording sphygmomanometer, *Jr. Lab. and Clin. Med.*, 1926, xii, 172.
15. WOOD, J. E., JR., and CASH, J. R.: Experimental hypertension—observations on sustained elevation of systolic and diastolic blood pressure in dogs, *Jr. Clin. Invest.*, 1936, xv, 543.
16. CASH, J. R., and WOOD, J. R., JR.: Observations upon the blood pressure of dogs following changes in body weight, *South. Med. Jr.*, 1938, xxxi, 270.
17. PROGER, S. H., and DENNIG, H.: A study of the circulation in obesity, *Jr. Clin. Invest.*, 1932, xi, 789.
18. WEISS, SOMA: The etiology of arterial hypertension, *ANN. INT. MED.*, 1934, viii, 296.
19. TERRY, A. H.: Obesity and hypertension, *Jr. Am. Med. Assoc.*, 1923, lxxxi, 283.

THE INFLUENCE OF IRON AND DIET ON THE BLOOD IN PREGNANCY *

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TRUE anemia of pregnancy may be defined as a condition characterized by decrease in red blood cells or hemoglobin or both below the levels which may be considered as physiologic for the period of gestation, such decrease being associated with and dependent upon the gravid state. It is to be distinguished from anemia coincidental with pregnancy such as may result from hemorrhage, infection or primary blood dyscrasia.

The significance of anemia of pregnancy lies in its prevalence, its effect upon the health of both mother and infant, its response to appropriate therapy and its preventability. Moreover, accurate blood examination as part of prenatal care derives its importance not only from the direct effects of such anemia as may be disclosed, but also from the possible evidence of deranged metabolic processes, which are often reflected by relatively slight deviations from the normal blood values.

The present communication deals with blood and dietary studies carried out on 158 pregnant women. Of these, observations on 133 were sufficiently frequent, including examinations made six weeks after delivery, and treatment sufficiently well carried out, to permit satisfactory evaluation of therapeutic measures. The subjects, attending the out-patient maternity service of the University Hospital, represent a fair cross-section of medium and low income groups. Most of them were residents in small urban communities and about 40 per cent received welfare assistance. The majority of the patients were in their early twenties but the range of ages was wide. Approximately two-thirds had had one or more children, and there was no evident relationship between parity and the incidence or severity of anemia.

Ninety-six members of the group were interviewed by a dietitian with the object of ascertaining dietary habits and their conditioning factors, and of correcting such habits where indicated in accordance with the special requirements of pregnancy and the ability of the patient to secure foods recommended. Subsequent consultations were held for the purpose of determining adherence to instructions and for further advice and adaptation of the diet to changing clinical conditions. The basic diet recommended for pregnancy is that formulated by the League of Nations Technical Commission.¹ It provides, in addition to other so-called protective foods in quantities considered adequate, a daily protein intake of approxi-

* Read at the New Orleans meeting of the American College of Physicians, March 29, 1939.

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mately 80 grams of which about 50 grams are supplied by meat, eggs, milk and milk products. Adequacy of vitamin B₁ (thiamin) has been set at an approximate minimum level of 15 units per 100 calories² and of riboflavin at a minimum level of about 500 units daily.³ The intake of nicotinic acid has been considered to parallel that of riboflavin.

All blood examinations were made on oxalated venous blood in accordance with a standard procedure previously described.⁴ Erythrocyte counts, hemoglobin estimations and packed cell volume hematocrit determinations were made, after the first ante-natal examination, at monthly intervals, whenever possible, throughout the remainder of the pregnancy, during labor, 10 days after delivery and 42 days after delivery.

The recognition and classification of anemia in association with any physiologic state, such as pregnancy, requires the preliminary establishment of standards of normality for that state. No wholly satisfactory standards for the blood values in pregnancy have as yet been formulated and among investigators there is considerable divergence of opinion regarding the minimum levels of the red blood cell count, hemoglobin and packed cell volume which may be considered normal for the pregnant woman. The increase in plasma volume which commonly accompanies gestation results in a diminished concentration of the corpuscular elements of the blood,⁵ and whereas this is usually more than compensated for in the case of the leukocytes, an increase of the red blood cells corresponding to that of the plasma commonly fails to occur. Assumed minimum levels for pregnancy based on the observed maximum degree of plasma dilution and the lower limit of the normal range for non-pregnant women are open to a number of objections, including the lack of knowledge in the majority of individual cases of either the pre-gravid blood level or the actual increase of plasma volume. Values that, in pregnancy, may be physiologic for one woman for another may indicate a pathologic trend. Tentative standards for average and minimum red blood cell and hemoglobin values in pregnancy have been determined on our subjects on the basis of evidence of return, within six weeks after delivery to non-pregnant normal levels, in the absence of medicinal or diet therapy. The detailed data from which these standard values are derived will be reported elsewhere. In brief, we regard an erythrocyte count of less than 3,500,000 per cubic millimeter or a hemoglobin value of less than 10.0 grams per 100 c.c. occurring at any time during pregnancy as evidence of true anemia (table 1).

The majority of instances of anemia of pregnancy appear to fall in the iron deficiency group. Yet normal gestation places no great demand upon maternal iron stores.⁶ The total additional requirement of iron incident to pregnancy does not exceed 250 milligrams or approximately the amount contained in 500 c.c. of blood. Consequently the high incidence of iron deficiency anemia among pregnant women indicates four possible etiologic factors: (1) prevalence of low iron reserves among non-pregnant women; (2) restricted utilization of reserve iron in satisfying maternal iron re-

quirements; (3) impaired absorption of dietary iron during gestation; (4) low intake of food iron. The two last mentioned conditions can hardly operate as sole or major causes of anemia during pregnancy.

It has been common experience that a considerable percentage of cases of anemia associated with pregnancy fail to respond satisfactorily to iron therapy. In previous reports of clinical⁴ and experimental⁷ studies evidence has been presented that such anemia is dependent upon deficiencies of the diet, and that it may be differentiated from iron deficiency anemia by

TABLE I
Tentative Standards of Normality for the Blood in Pregnancy
Average Normal Blood Values

	Month of Pregnancy						During Labor	10 Days Post-partum	42 Days Post-partum
	4	5	6	7	8	9			
R.B.C.	4.47	4.20	3.93	3.94	4.02	4.04	4.41	4.48	4.75
Hgb.	11.8	11.4	11.0	11.1	11.2	11.2	11.9	12.6	13.2
Hct.	39.5	38.9	37.0	36.8	37.3	37.1	39.3	42.1	42.7
M.C.Hb.	26.2	27.1	28.2	28.4	28.0	28.0	27.2	28.0	27.4
C. I.	.90	.93	.97	.98	.96	.96	.93	.96	.94
M.C.V.	88	93	95	94	93	93	89	94	90
V. I.	.98	1.04	1.06	10.5	1.04	10.4	1.00	1.05	1.01
M.C.Hb.Conc.	29.8	29.4	29.7	30.2	30.2	30.2	30.3	30.0	30.9
S. I.	.91	.86	.91	.92	.92	.92	.92	.92	.94

Minimum Normal Erythrocyte and Hemoglobin Values

R.B.C.	3.8	3.7	3.6	3.5	3.6	3.8	4.0	4.0	4.2
Hgb.	10.7	10.5	10.2	10.1	10.2	10.5	10.8	10.8	12.0

morphologic criteria. The basis of classification of the common anemias of pregnancy which we employ is as follows:

Iron deficiency anemia: Hemoglobin below 10.0 grams per 100 c.c.

Mean corpuscular hemoglobin below 26 micro-micrograms.

(Color index below 0.9.)

Diet deficiency anemia: Red blood cell count below 3.5 million per cu. mm.

Mean corpuscular volume above 97 cubic microns.

(Volume index above 1.1.)

Anemia of pregnancy associated with inadequate food intake is a true macrocytic anemia and in its more severe manifestations is probably identical with the so-called "pernicious anemia" of pregnancy.⁸ Although it has been reported that deficiency of the vitamin B complex may lead to such anemia^{9, 10} our results indicate that a closer correlation exists between the incidence of macrocytic anemia and inadequate intake of animal protein than between such anemia and deficiency of either thiamin, riboflavin or the pellagra preventing factor (table 2).

TABLE II

The Relationship of Macrocytic Anemia to the Intake of Animal Protein and the Vitamin B Complex during Pregnancy

Diet	Incidence of Macrocytic Anemia Per Cent
Daily intake of animal protein above 50 grams.....	00.0
Daily intake of animal protein between 30 and 50 grams.....	27.3
Daily intake of animal protein below 30 grams.....	40.0
Daily intake of Vitamin B ₁ (Thiamin)—adequate.....	7.9
Daily intake of Vitamin B ₁ (Thiamin)—inadequate.....	28.9
Daily intake of Vitamin B ₂ Complex—adequate.....	9.4
Daily intake of Vitamin B ₂ Complex—inadequate.....	29.3

In table 3 is given an analysis with respect to incidence and type of anemia of the subjects included in the present study.

TABLE III

Incidence and Type of Anemia of Pregnancy among the Subjects Included in the Present Study

	Number	Per Cent
Cases included in study.....	158	100.0
Cases with iron deficiency anemia.....	42	26.6
Cases with diet deficiency anemia.....	24	15.2
Cases with combined deficiency anemia.....	19	12.0
Total cases with anemia.....	85	53.8

Before attempting the evaluation of any form of treatment of anemia during pregnancy an appreciation should be gained of the normal trend of blood values throughout gestation. As stated previously, these changes have been shown to depend, in part, upon varying dilution of the plasma, but that such hydremia is not the only factor responsible for the "physiologic" anemia of pregnancy is indicated by the universal tendency in apparently normal subjects of the mean corpuscular hemoglobin (color index) to decrease appreciably, especially during the early months of gestation, and of the mean corpuscular volume (volume index) to undergo a slight increase. Even in the presence of anemia, untreated, there is usually an

increase in the red blood cells and hemoglobin during the latter months of pregnancy. However, such changes are probably chiefly the mechanical effect of varying concentration, and if observations are made six weeks after delivery it will usually be found that the blood values, especially the hemoglobin, are definitely below the normal range. The trends of erythrocyte and hemoglobin determinations from the beginning of the fourth month of pregnancy to that of the seventh week post partum are shown on chart 1.

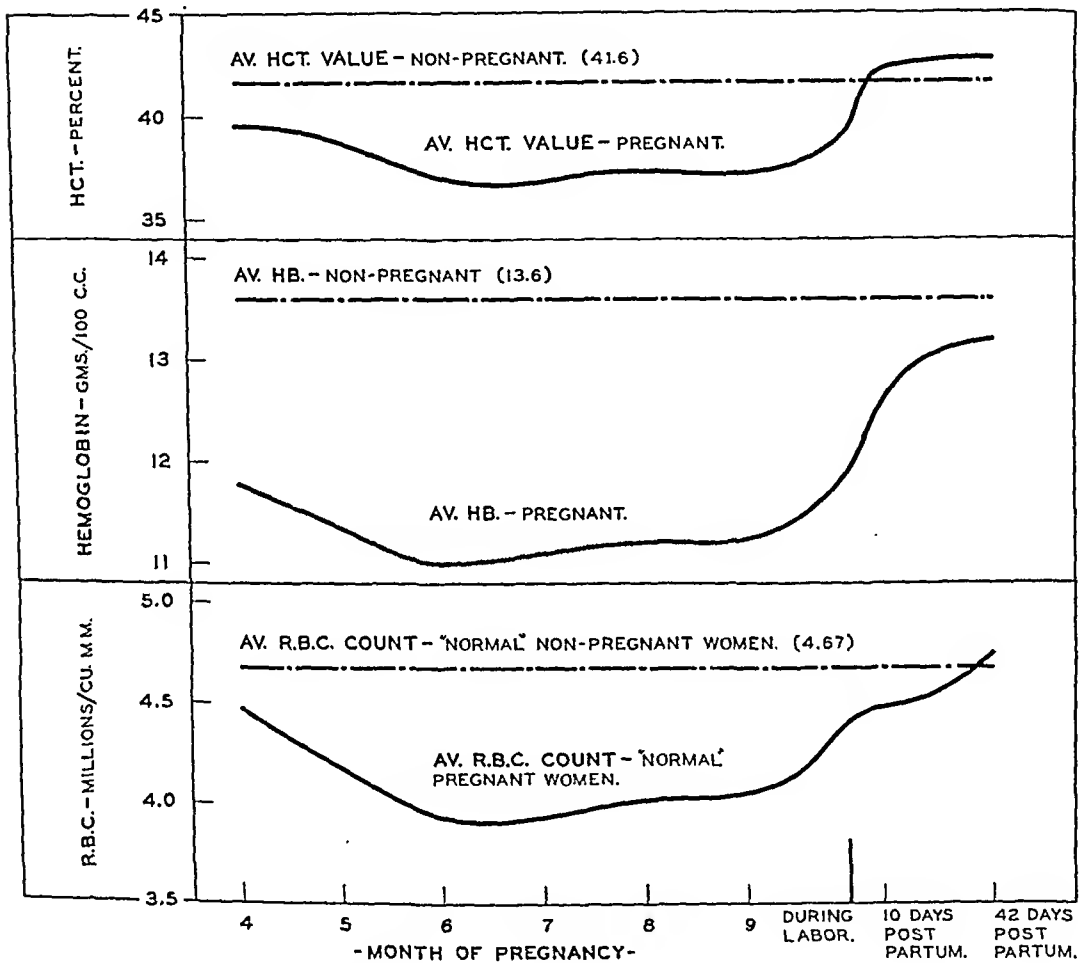


CHART 1. The "physiologic" anemia of pregnancy. Average values based on observations of 30 pregnant women who received no anti-anemia therapy and whose erythrocyte, hemoglobin, and packed cell volume determinations made six weeks after delivery were within normal limits for non-pregnant women. The average normal values for non-pregnant women given here are based on observations at the Simpson Memorial Institute of 100 healthy subjects within the age group of the patients studied.

To determine the effects of iron therapy* the following procedure was employed: 42 subjects with hypochromic anemia and normal or small red blood cells were divided into two groups; to the members of one, comprising 19, ferrous sulphate 0.32 gram three times daily was given, for those of the other, 23 cases, no iron was prescribed. The definite value of medicinal

* The iron preparation employed in this study was supplied by the Eli Lilly Company.

iron for this form of anemia is illustrated in chart 2. Since the period of gestation at which iron therapy was instituted varied between the fifth and eighth months, the contrast between the two groups is best shown by the observations made six weeks after delivery, when the members of the treated group were within the range for normal non-pregnant women, with respect to average erythrocyte and hemoglobin determinations, whereas those of the untreated group possessed hemoglobin values averaging 2.6 grams lower than those of the treated subjects. The positive and controlled therapeutic results obtained on these patients appear to us to disprove the contention

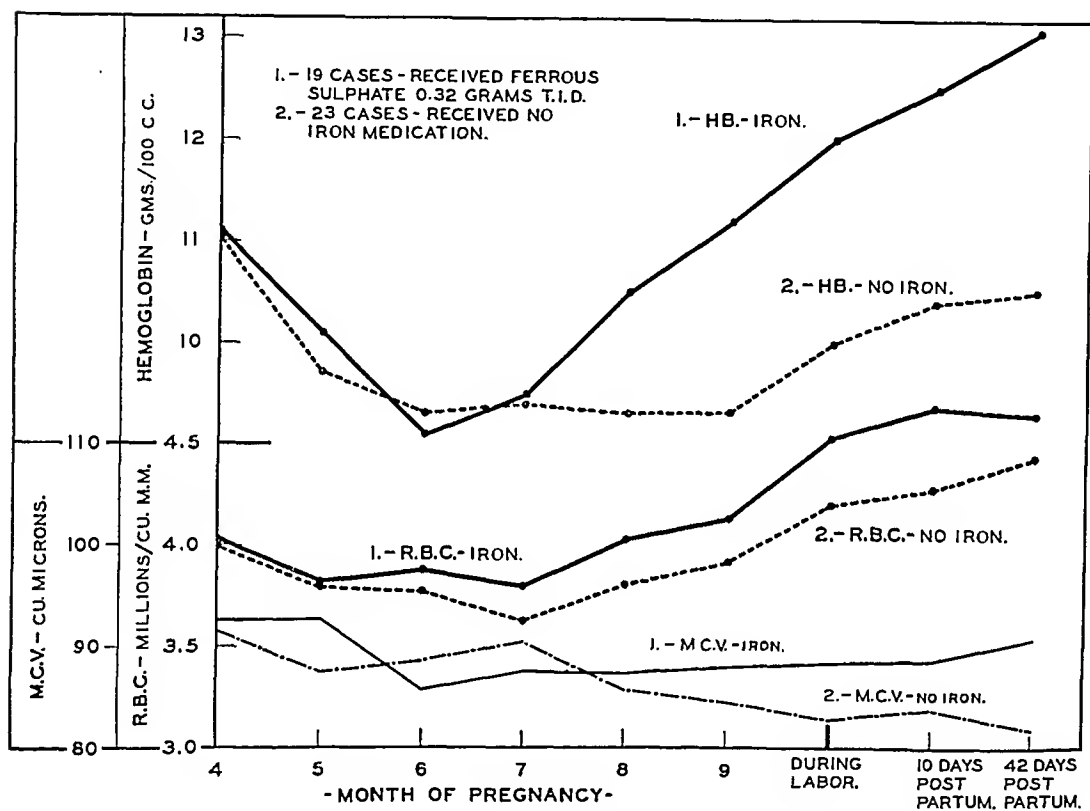


CHART 2. Comparison of the effects of medicinal iron and no therapy on the average erythrocyte, hemoglobin and mean corpuscular volume values of pregnant women with anemia attributed to iron deficiency.

that during pregnancy decline of the hemoglobin to levels appreciably below 10.0 grams per 100 c.c. can be considered physiological.¹¹ Further evaluation of iron medication in pregnancy was attempted by the selection of 50 women considered, by our standards, to have blood values within the normal range for pregnancy. As in the previous experiment these subjects were divided into two groups of 27 and 23 cases each, and received, respectively, ferrous sulphate and no iron (chart 3). At six weeks post partum the iron treated group possessed an average hemoglobin value 0.3 gram higher than the untreated subjects, but the wider divergence of average hemoglobin determinations at the tenth day post partum suggests that many patients

considered as "normal" with respect to hemoglobin, may nevertheless benefit from iron medication. These observations lead us to agree with the contention of Corrigan and Strauss that routine iron administration throughout pregnancy is justifiable.¹²

The effects of diet improvement on the blood values of 25 patients with macrocytic anemia were determined by dividing the subjects into four groups: (1) six subjects received diet therapy and no iron; (2) seven subjects received no diet instructions and no iron; (3) seven subjects re-

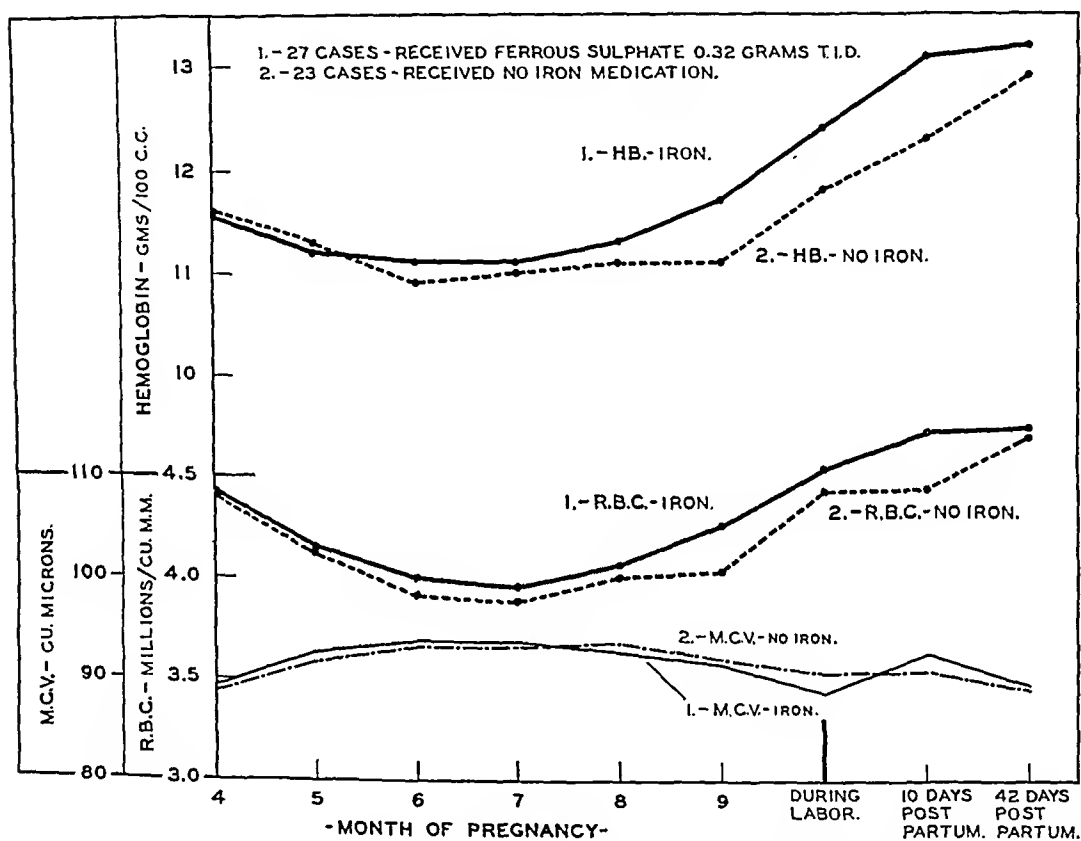


CHART 3. Comparison of the effects of medicinal iron and no therapy on the average erythrocyte, hemoglobin and mean corpuscular volume values of pregnant women without demonstrable anemia.

ceived diet therapy and iron; (4) five subjects received no diet therapy but were given iron.

The hematologic observations on these cases are presented in charts 4 and 5. It should be pointed out that, because of the multiplicity of factors involved and the variable adherence to diet instructions, evaluation of the results of diet therapy in a group of cases is more difficult and somewhat less satisfactory than a similar analysis of the effects of a single form of medication such as iron. Nevertheless, it is clear that improvement in the diet, particularly with respect to the intake of animal protein, was followed by significant increase in blood values, in comparison with the control

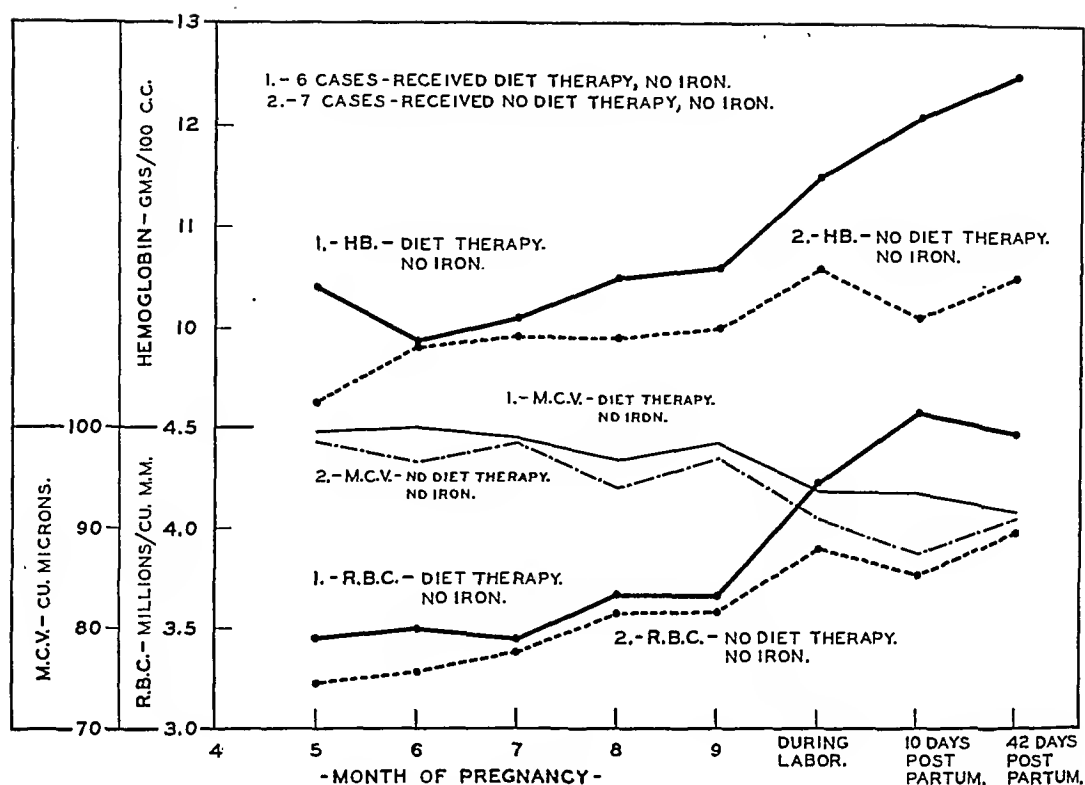


CHART 4. Comparison of the effects of diet improvement, particularly with respect to increased intake of animal protein, and no therapy, on the average erythrocyte, hemoglobin, and mean corpuscular volume values of pregnant women with anemia attributed to dietary deficiency.

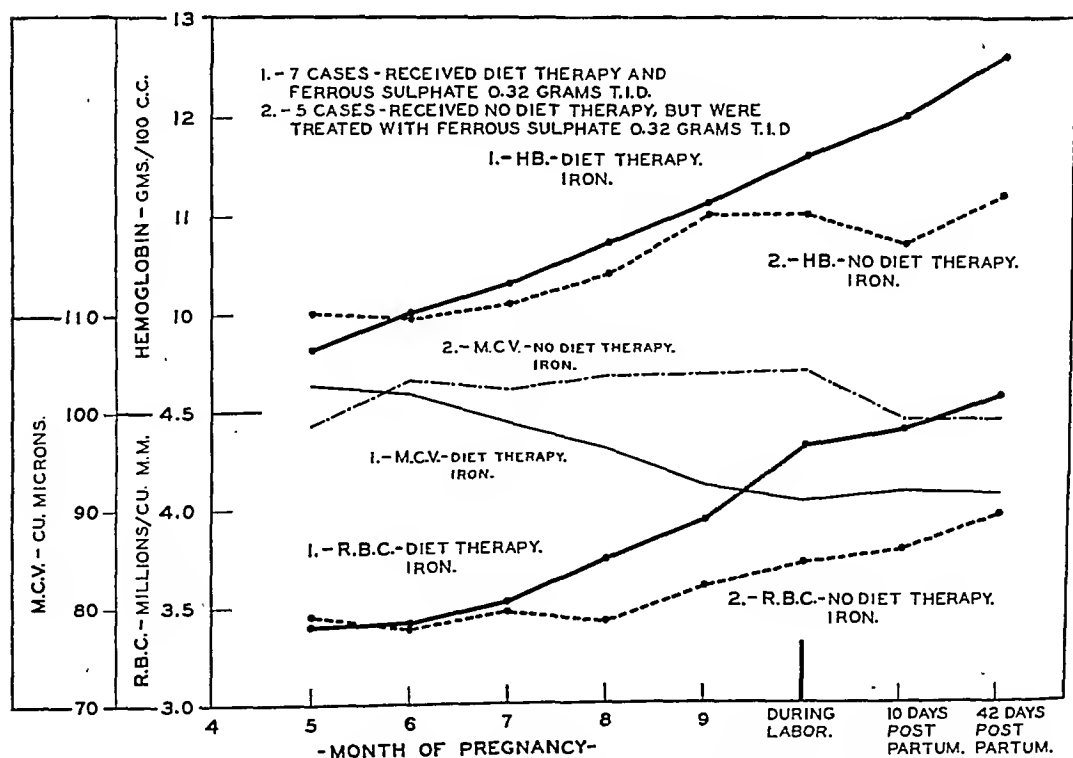


CHART 5. A study similar to that shown on Chart 4 except that all subjects were given medicinal iron.

groups, whether or not iron was also prescribed. However, the more uniform rate of increase of both red blood cells and hemoglobin when iron was given in conjunction with improved diet suggests that the metal may be of supplementary value in the treatment of anemia of pregnancy attributed to dietary deficiency.

CONCLUSIONS

The incidence of true anemia of pregnancy is high, amounting to 54 per cent of 158 clinic cases studied. Such anemia most often results from deficiency or impaired utilization of iron. A second important cause is inadequacy of the diet, particularly with respect to its content of animal protein.

Hemoglobin values, in pregnancy, below 10.0 grams per 100 c.c. are probably never "physiological," and in the presence of lowered mean corpuscular hemoglobin or color index indicate a lack of available iron. Red blood cell counts below 3,500,000 per cubic millimeter associated with macrocytosis suggest protein deficiency. Not infrequently a combined type of anemia is present, presumably dependent upon a need for both iron and protein.

Inorganic ferrous preparations are the most effective and least irritating forms of medicinal iron for use in the treatment of the hypochromic anemia of pregnancy. Since the detection of slight degrees of iron deficiency during gestation is difficult, and the evidence presented indicates that the majority of pregnant women derive benefit from iron medication, it is justifiable to administer iron routinely throughout pregnancy.

A diet supplying approximately 50 grams of animal protein daily, in addition to adequate amounts of other "protective" foods, is effective in correcting anemia of moderate degree attributed to dietary deficiency. In the treatment of more severe macrocytic anemia of pregnancy the daily intake of animal protein should be adjusted to a level of 1.5 grams per kilo.

BIBLIOGRAPHY

1. League of Nations Health Comm. Tech. Commission, Rep. on Physiological Bases of Nutrition, 1935, London.
2. COWGILL, G. R.: Human requirements for vitamin B₁, Jr. Am. Med. Assoc., 1938, cxi, 1009.
3. SHERMAN, H. C., and SANFORD, C. S.: Riboflavin: dietary sources and requirements, Jr. Am. Med. Assoc., 1938, cx, 1228.
4. BETHELL, F. H.: The blood changes in normal pregnancy and their relation to the iron and protein supplied by the diet, Jr. Am. Med. Assoc., 1936, cvii, 564.
5. DIECKMANN, W. J., and WEGNER, C. R.: The blood in normal pregnancy: blood and plasma volumes, Arch. Int. Med., 1934, liii, 71.
6. FULLERTON, H. W.: Anaemia in poor class women with special reference to pregnancy and menstruation, Brit. Med. Jr., 1936, ii, 523. Hypochromic anaemias of pregnancy and puerperium, Ibid., 1936, ii, 577.
7. KYER, J., and BETHELL, F. H.: Production of macrocytic anemia in the pregnant rat by diets low in protein, Arch. Path., 1938, xxv, 767.

8. GOLDHAMER, S. M.: "Pernicious anemia" of pregnancy, *Proc. Cent. Soc. Clin. Res.*, 1938, page 45.
9. WILLS, L.: Studies in pernicious anaemia of pregnancy; tropical macrocytic anaemia as deficiency disease with special reference to vitamin B complex, *Indian Jr. Med. Res.*, 1934, xxi, 669.
10. ELSOM, K. O.: Macrocytic anemia in pregnant women with vitamin B deficiency, *Jr. Clin. Invest.*, 1937, xvi, 463.
11. WATSON, H. G.: The blood picture of pregnancy, *Am. Jr. Obst. and Gynec.*, 1938, xxxv, 106.
12. CORRIGAN, J. C., and STRAUSS, M. D.: The prevention of hypochromic anemia in pregnancy, *Jr. Am. Med. Assoc.*, 1936, cvi, 1088.

TREATMENT OF THE STOKES-ADAMS SYNDROME BY HYPERTONIC GLUCOSE SOLUTION GIVEN INTRAVENOUSLY *

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ALTHOUGH the symptom complex grouped under the heading of the Stokes-Adams syndrome may be caused by many conditions which produce temporary cerebral anemia, we will confine our discussion only to the two main conditions, namely stoppage of the heart and ventricular fibrillation. Furthermore, we shall eliminate from our discussion those cases of sino-auricular standstill or auriculo-ventricular block caused by direct or reflex vagal inhibition which can be abolished or successfully treated by atropine. This leaves us a group of cases where for some unknown reason there is a sudden interruption in the passage of the electrical impulse from the auricles to the ventricles, resulting in complete ventricular stoppage, or the sudden onset of ventricular fibrillation. The condition usually occurs in individuals where partial auriculo-ventricular block already exists.

The treatment of the condition has been unsatisfactory in the past, and the effects of the therapeutic measures employed have been contradictory. Barium chloride has long been discarded as useless. Adrenalin and ephedrine have been found to have beneficial effects in cases where the ventricles stop, but some investigators as Dock¹ and Schwartz and Jezer² found that these drugs may induce attacks of ventricular fibrillation. On the other hand, some authors as Phear and Parkinson,³ Levine and Matton⁴ and Cahall⁵ claim good results from adrenalin even in ventricular fibrillation. The use of quinidine in ventricular fibrillation likewise has its supporters and antagonists. Levine⁶ found experimentally that quinidine prevents ventricular fibrillation. Dock¹ and Escamille⁷ found it of value in clinical ventricular fibrillation. Kerr and Bender,⁸ Schwartz and Jezer,⁹ Davis and Sprague¹⁰ and Cahall⁵ on the other hand found that the drug induces ventricular fibrillation. In one of my cases of Stokes-Adams syndrome due to transient ventricular fibrillation, both quinidine sulphate and adrenalin brought about attacks with greater frequency, and each attack was more prolonged and more severe. In another case adrenalin seemed to have good effects.

One of the reasons for our therapeutic inefficiency in this condition is that we do not know what changes take place in the heart which bring about the sudden interruption of conduction or the sudden onset of ventricular fibrillation. That vagal hyper-activity plays no part is evidenced by the fact that no amount of atropine given during an attack relieves the condition. It appears to be due to local circulatory stasis and edema of the auriculo-ventricular node, the bundle and bundle branches, resulting in sudden inter-

* Received for publication September 14, 1937.

ference with nutrition and oxygenation of this delicate apparatus. This could conceivably produce disturbances in conduction and in some cases the initiation of multifoci of irritability culminating in a circus movement in the ventricles and ventricular fibrillation. The circulatory changes may be analogous to those seen in partial occlusive vascular disease of the extremities.

If this conception is correct, a concentrated solution of any crystalloid injected intravenously which would tend to act as a tissue dehydrant should give relief. Of these a concentrated glucose solution appeared to me to be the best for the purpose. Since its value was first demonstrated in the relief of intraocular tension in glaucoma by Hertel¹¹ in 1915, and in the relief of increased cerebro-spinal pressure by Weed and McKibben¹² in 1919, many reports appeared in the literature substantiating its value as a tissue dehydrant. I felt that in addition to its dehydrating effect it also has nutritive value. I have accordingly tried the use of 50 c.c. of a 50 per cent glucose solution, administered intravenously in four cases of Stokes-Adams syndrome. All four exhibited auriculo-ventricular dissociation, two with complete stoppage of the ventricles and two with ventricular fibrillation. The results appear to be very promising.

Although concentrated glucose solution given intravenously is used in some cardiac conditions, I did not find any reference of its use in the Stokes-Adams syndrome. For this reason and with the hope that it may prove to be of value in the treatment of this desperate condition, I offer this communication.

The following are short summaries of the four cases. Electrocardiographic studies of Case 1 and Case 3 were reported in full detail elsewhere.^{13, 14}

CASE REPORTS

Case 1. L. F., male, 58 years old, was first seen by me on March 7, 1936. He presented at that time definite clinical and electrocardiographic evidence of arteriosclerotic heart disease with the anginal syndrome. There was partial auriculo-ventricular block and marked delay in the intraventricular conduction time. Under appropriate therapy he showed improvement in his subjective symptoms until November 11, 1936, when he was found in the bathroom in an unconscious state and in convulsions. Since then there was a gradual and progressive increase in frequency, severity and duration of attacks of unconsciousness and convulsions. Some days he had as many as 20 such attacks in 24 hours. An electrocardiogram taken just before and during one of these attacks showed complete auriculo-ventricular dissociation, multifoci ectopic ventricular impulses followed by ventricular fibrillation. During the fibrillatory period, no heart sounds could be heard, and unconsciousness and convulsions would ensue. Quinidine sulphate aggravated the condition as did adrenalin and ephedrine. On December 22, he received 50 c.c. of 50 per cent glucose solution intravenously. During that day the attacks greatly diminished in intensity and frequency. There were merely transient dizziness and short periods of stupor but only very occasionally were there complete unconsciousness and convulsions. He was getting along fairly well for about 10 days thereafter on an occasional repetition of the intravenous glucose. On the eleventh day, however, he suddenly died during an attack of convulsions.

Case 2. J. A., male, 57 years old, who claimed to have been in good health previously, suddenly developed precordial pain and recurring attacks of transient loss of consciousness, some of which were rather prolonged and accompanied by convulsions. He was admitted to my service at the Harbor Hospital. The heart between the attacks showed a regular sinus rhythm with a rate of about 96 to 105 beats per minute, and there was no enlargement. The first sound was muffled and hardly audible, and there was a presystolic gallop rhythm. The second heart sound was likewise very weak. The electrocardiogram (figure 1) during an attack showed a sudden change

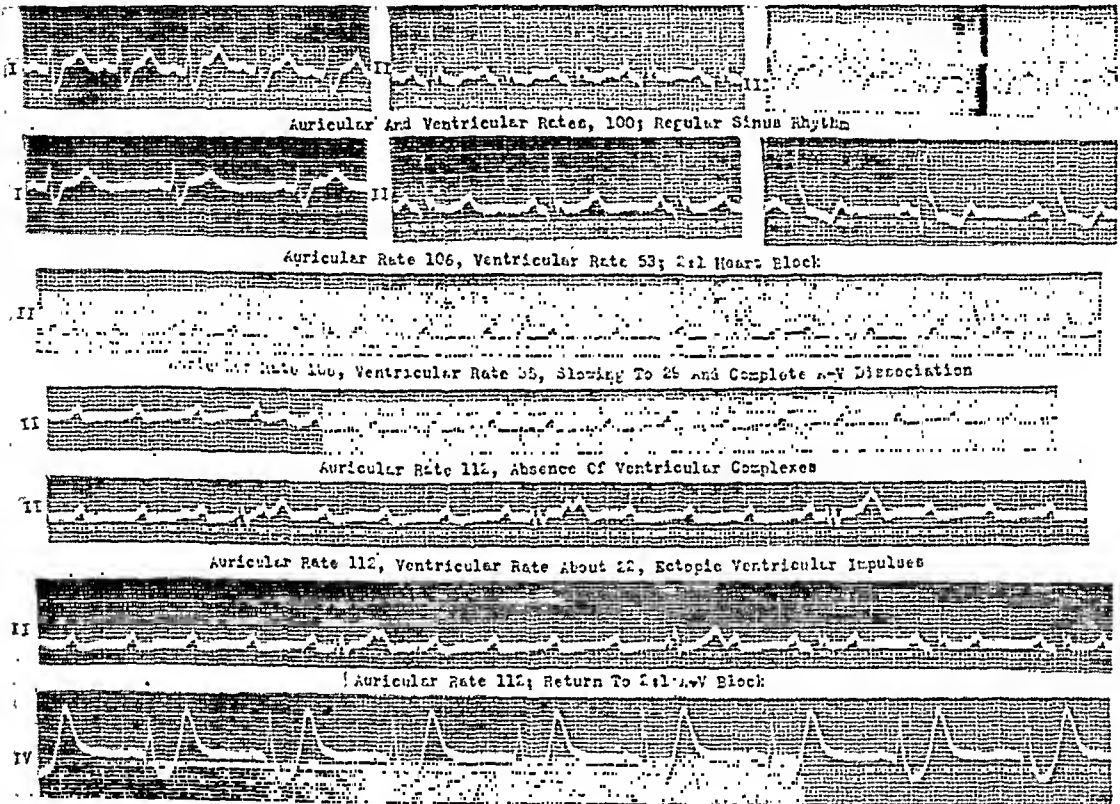


FIG. 1. *Electrocardiograms in Case 2.* Regular sinus rhythm with normal auriculo-ventricular conduction time followed by partial, then by complete auriculo-ventricular dissociation, and ventricular standstill. The intraventricular conduction time is about 0.15 second. The reappearance of the ventricular impulses are at first of the ectopic type and are later followed by the regular supraventricular type. The fourth lead (old standard method) shows grossly abnormal complexes associated with acute coronary occlusion.

from regular sinus rhythm and normal auriculoventricular conduction to partial 2:1 block and then a gradual increase in block with slowing of the ventricles until complete auriculoventricular dissociation and stoppage of the ventricles ensued. At this period loss of consciousness would occur followed by convulsions if the ventricles were at a standstill for half a minute or longer. These episodes of unconsciousness and convulsions recurred at very frequent intervals, at times as many as four attacks in one hour.

Because of the suddenness of onset with precordial pain and the disturbed auriculo-ventricular condition, the diagnosis was made of acute coronary occlusion, affecting most likely the right coronary artery and the ramus septi fibrosi.

An intravenous injection of 50 c.c. of 50 per cent glucose was given with almost miraculous results. There was no recurrence of auriculo-ventricular block. He re-

mained in the hospital nine weeks, and showed the characteristic clinical manifestations of acute coronary occlusion, that is, apical pericardial friction rub on the second day, temperature reaction, high leukocyte count and rapid sedimentation rate. The electrocardiogram likewise showed characteristic changes. At no time during those nine weeks did he have any recurrence of the Stokes-Adams syndrome. The rhythm was of normal sinus origin, rate about 80 to 96, and the auriculo-ventricular conduction time remained normal. The last I heard from him, about three months after his discharge from the hospital, was that he felt well.

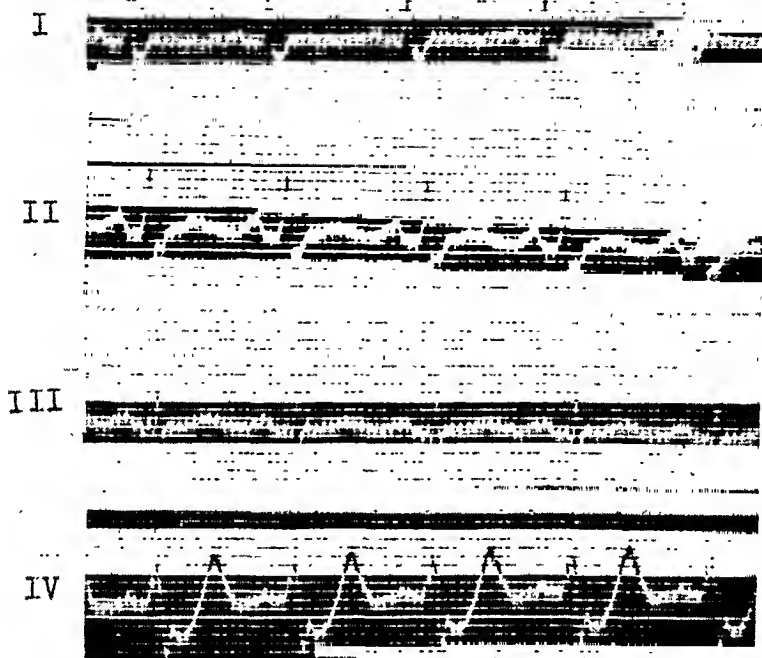


FIG. 2. Same case, one week later. Regular sinus rhythm with normal auriculo-ventricular conduction time. There are changes in the ventricular complexes in all leads, as compared with the previous tracings.

Case 3. E. S., female, 66 years old, seen by me on May 30, 1937, had mild diabetes for 10 years and hypertension for at least seven months. During the latter period she had recurring episodes of the anginal syndrome associated with ringing in the ears, and in four weeks she had four attacks of unconsciousness and convulsions. The first one recurred almost continuously for about five hours and was finally relieved by 1 c.c. of adrenalin given subcutaneously. The attacks recurred three days after and became very frequent. Any slight manipulation such as taking the blood pressure would induce an attack. There was complete auriculo-ventricular dissociation with an idioventricular rhythm of the supraventricular type and intra-ventricular block. Multifoci ectopic ventricular impulses occurred followed by periods of ventricular fibrillation. During the fibrillatory period the heart sounds were not audible, the pulse could not be felt and unconsciousness and convulsions ensued. The attacks became milder and recurred less frequently the following three days after repeated intravenous injections of 50 c.c. of 50 per cent glucose solution were given. For three weeks thereafter there was no recurrence of the Stokes-Adams syndrome. She finally died during a severe attack.

Case 4. S. J., male, 67 years old, with a history of hypertension for many years, suddenly became unconscious and went into convulsive seizures while at rest in bed. These attacks recurred about eight times in the following 24 hours and became more severe and prolonged each time.

He presented generalized arteriosclerosis. The heart was moderately enlarged to the left and the aortic arch was markedly widened. A harsh systolic murmur was heard at the third left costosternal junction transmitted to the base, neck and downwards as far as the apex. The heart rate between attacks was 76, rhythm regular. There was a prolongation of P-R conduction time to 0.26 sec. At the onset of the attack there was a gradual prolongation of the P-R conduction time to as high as 0.48 second, with a dropping out of ventricular beats and soon there was complete stoppage of the ventricles while the auricles continued beating at the same rate as previously. During this period, unconsciousness and convulsions would occur. There was no evidence of failure of either the right or left ventricle.

Glucose solution given intravenously resulted in complete stoppage of attacks. Two months have now elapsed with no recurrence of complete block and the Stokes-Adams syndrome. The rhythm is of regular sinus origin but the P-R conduction time is still 0.26 second. Aside from the anginal syndrome in a moderate degree, he is fairly comfortable.

COMMENT

Because the Stokes-Adams syndrome has a tendency to subside spontaneously for variable periods, our conclusions as to the value of any medication in this condition must be guarded. There is, however, no doubt that the four cases recorded in this paper on whom hypertonic glucose solution was used have definitely benefited by it.

That the benefit is not permanent, and that sooner or later termination of life by the disease will ensue is to be expected from the nature of the underlying pathology. The four patients presented here all had advanced arteriosclerotic heart disease which is a progressive condition. In all these cases, constant physiologic changes undoubtedly occur in the vascular supply to the heart muscle in the form of stasis, venous engorgement, transient spasm and so on. For this reason any medication which might be of benefit can not be well timed in its application. We can employ it only when gross subjective or objective manifestations of disturbances are evident. We must, therefore, not expect the use of hypertonic glucose solution to be always successful in preventing attacks. If it affords relief and prolongs life, however, it is worth further trial in as serious and often as hopeless a condition as the Stokes-Adams syndrome.

This method of treatment is definitely more efficacious in Stokes-Adams syndrome caused by ventricular stoppage than that caused by ventricular fibrillation. In the former condition it appears to have a permanently beneficial effect, judging from the two cases recorded here.

I have not had the opportunity to try it in younger individuals where the heart disturbance may be caused by infections. In such instances it will probably prove to be of greater value.

REFERENCES

1. DOCK, W.: Transitory ventricular fibrillation as a cause of syncope and its prevention by quinidine sulphate, *Am. Heart Jr.*, 1928-29, iv, 709.
2. SCHWARTZ, S. P., and JEZER, A.: The action of adrenalin on patients with complete heart block and Stokes-Adams seizures, *Am. Heart Jr.*, 1932, vii, 652.
3. PHEAR and PARKINSON, J.: Adrenalin in the Stokes-Adams syndrome, *Lancet*, 1922, i, 933.
4. LEVINE, S. A., and MATTON, M.: Observations on a case of Adams-Stokes syndrome showing ventricular fibrillation and asystole lasting five minutes with recovery following the intracardiac injection of adrenalin, *Heart*, 1925-26, xii, 271.
5. CAHALL, W. L.: Paroxysmal ventricular fibrillation, *Jr. Am. Med. Assoc.*, 1935, cv, 2054.
6. LEVINE, H. D.: Effect of quinidine sulphate in inhibiting ventricular fibrillation, *Arch. Int. Med.*, 1932, xlix, 808.
7. ESCAMILLE, R. F.: Report of case of paroxysmal ventricular fibrillation—quinidine therapy, *Am. Heart Jr.*, 1932, viii, 850.
8. KERR, W. J., and BENDER, W. L.: Paroxysmal ventricular fibrillation with cardiac recovery in a case of auricular fibrillation and complete heart block while under quinidine sulphate therapy, *Heart*, 1922, ix, 269.
9. SCHWARTZ, S. P., and JEZER, A.: The action of quinidine in ventricular fibrillation, *Am. Heart Jr.*, 1933-34, ix, 792.
10. DAVIS, D., and SPRAGUE, R.: Ventricular fibrillation: its relation to heart block, *Am. Heart Jr.*, 1929, iv, 559.
11. HERTEL, E.: Klinische Untersuchungen über die Abhängigkeit des Augendruckes von der Blutbeschaffenheit, *Arch. f. Ophth.*, 1915, xc, 309.
12. WEED, L. H., and McKIBBEN, P. S.: Pressure changes in the cerebro-spinal fluid following intravenous injections of solutions of various concentrations, *Am. Jr. Physiol.*, 1919, xlviii, 512.
13. SIGLER, LOUIS H.: Adams-Stokes syndrome induced by transient recurrent ventricular fibrillation, *Am. Heart Jr.*, 1938, xvi, 109.
14. SIGLER, LOUIS H.: The fibrillatory phase of transient recurrent ventricular fibrillation, *Internat. Clin.*, 1939, i, 221-226.

SUDDEN AND UNEXPECTED DEATH FROM ACUTE INTERSTITIAL MYOCARDITIS; A REPORT OF THREE CASES *

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THE causes of sudden and unexpected death occurring in individuals in apparent good health frequently require microscopic study for their elucidation. A miniature or inconspicuous lesion may be the main factor in such a type of death with the result that sometimes painstaking search is required to find it. Such cases are not only of scientific interest but they may have far reaching forensic implications.

Focal interstitial myocarditis as the cause of death is a relatively uncommon condition and, as the cause of sudden and unexpected death, it appears from the study of the reported cases to be quite rare. Simon and Walpaw¹ recorded 48 cases in 1935 and added one of their own. Since then Scott and Simon,² Hirai³ and Kjaergaard⁴ have reported single cases, making a total of 52 in the literature to 1938 which had been proved by necropsy studies. In this group there were but eight instances where death was more or less sudden in character.

Recently we have studied three cases of sudden and unexpected death in which the mechanism was acute cardiac failure with pulmonary edema and the cause of this cardiac death was discovered only after careful microscopic study of the myocardium.

CASE REPORTS

Case 1. Mr. C. E. B. H., 32 years old, an electric driller, was working on a scaffold about 10 feet from the ground when he suddenly fell down on the scaffolding unconscious. When first examined by a physician his heart was not beating and adrenalin injected into the left ventricle failed to produce any palpable or audible cardiac impulse. He was taken to a hospital where he was pronounced dead. Interrogation of his family and associates was negative for any history of previous illnesses. Because of the fact that he was working with an electric drill, the possibility of electrocution was considered and on careful investigation of the drill a short circuit was found. It was the impression of those who saw the entire picture of the sudden fall that he died instantaneously or at least very shortly after the fall.

NECROPSY

Examination was performed 16 hours after death. The arterial embalming had been done within one hour after death. At the necropsy examination the subject was found to be a very large man weighing about 210 pounds and measuring about 6 feet 1 inch in length. The only findings of interest were confined to the chest. The heart weighed 410 grams and showed a moderate degree of dilatation of all the chambers. There was a persistent thymus present and the aorta was a typical *aorta*

* Received for publication April 15, 1938.

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angusta. No blood was present in the pericardial sac even though the needle puncture had penetrated into the right ventricle thus suggesting that the heart had stopped beating when the adrenalin was administered. There were about 50 c.c. of free fluid in each pleural cavity and the lungs were the seat of marked edema and clear frothy fluid poured forth from the cut surface. There was an intense acute hyperemia of all the viscera. One small hemorrhage about the size of a quarter of a dollar was found in the pulmonary parenchyma. No other abnormalities were encountered after a thorough search except for two small red spots above each external malleolus and above each radial prominence on both wrists. These measured from three to four millimeters in diameter and were moderately desiccated. The question of possible current marks was eliminated by subsequent histological examination and inasmuch as a depression was present on the skin in these regions it was considered that they

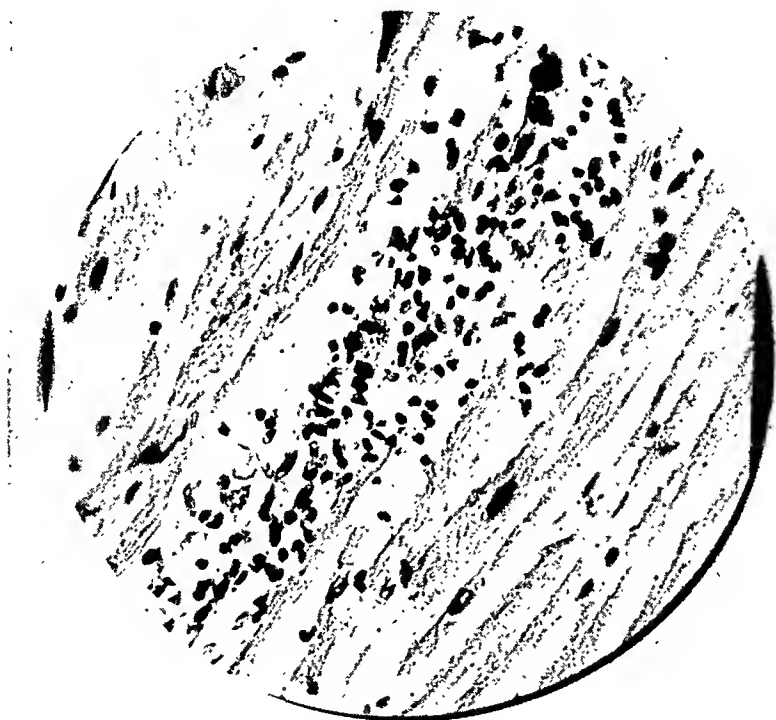


FIG. 1. *Case 1*. High power photomicrograph showing focus of interstitial inflammation in the myocardium.

represented areas where the hands and feet had been tied with cord after death. The brain and spinal cord were negative.

Histologic Pathology. The heart muscle fibers were hypertrophied and about many of the small blood vessels there was a mild degree of interstitial edema. A rather striking segmentation of many of the muscle fibers was also found. Some of the small blood vessels showed swelling of the intimal endothelium. A rare focus of acute and chronic inflammatory cells was found after prolonged search. These foci showed breaking up and disintegration of the muscle fibers. The inflammatory cells in these foci were largely mononuclear cells although occasional polymorphonuclear leukocytes and plasma cells were seen. There was loss of cross striation of the muscle fibers in these foci and in the body of the fiber, granular changes and fragmentation of the cytoplasm were seen. The auricular muscle showed scattered round cells in the stroma between the fibers.

The lung showed dilatation of the inter-alveolar capillaries from acute congestion and the larger vascular channels were likewise engorged. In some of the alveoli a homogeneous pink albuminous precipitate was found.

The other viscera showed nothing histologically noteworthy.

Case 2. Mr. P. B., 43 years old, a laborer, on the day of his death had been painting the inside of a tank with gilsonite asphaltum paint. The paint was thinned with petroleum naphtha. A heavy stream of air was running through the tank at all times and he was in the tank on only two occasions at intervals of ten and eight minutes respectively. Four other men were working in the tank painting and none of them suffered any untoward symptoms. He emerged from the tank with his partner and rested some 30 minutes, worked around the plant in the open air for about

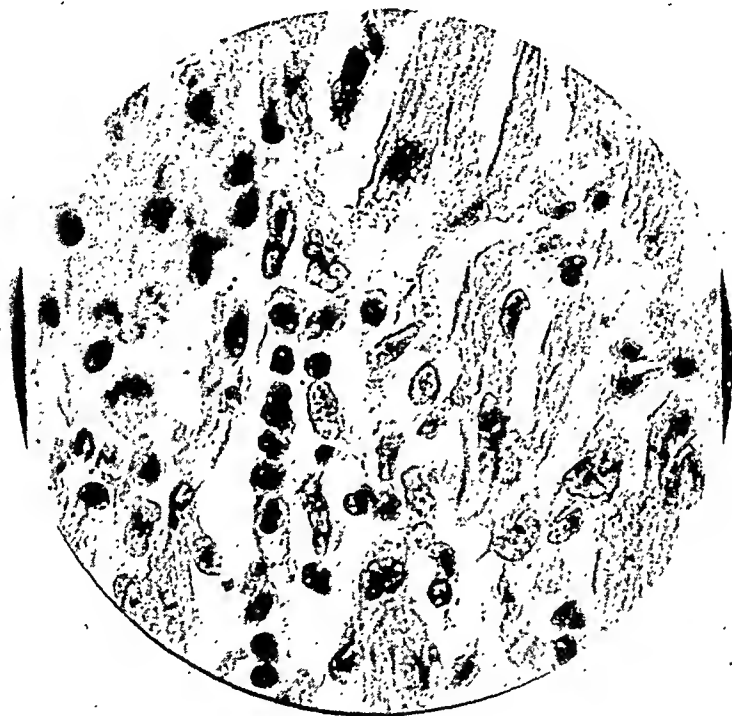


FIG. 2. *Case 2.* Oil immersion photomicrograph showing myocardial inflammation. Note character of cells and breaking up of muscle fibers.

an hour and then went home with a friend. At no time during the period when he was working in the tank or thereafter while working about the plant did he complain or show any visible evidence to his associates of anything abnormal in his behavior. When he arrived at home, his wife stated that he fell to his knees when he entered the front door, began to froth at the mouth and suffered paroxysms of coughing. A doctor was summoned who gave him morphine and atropine which produced temporary relief. An examination of his chest at this time revealed signs of advanced pulmonary edema. Two hours after this paroxysm another of similar character occurred and morphine and atropine were again administered, this time without much relief. Shortly thereafter the patient began to show signs of more striking pulmonary edema and died. He arrived home about five o'clock in the evening and died about eleven o'clock that night. The only possibly significant history obtainable was to the effect that eleven years previously he had been in a hos-

pital for a few days because of an attack of the influenza. At this time the hospital record showed that he had an irregular pulse. No other history was obtainable of any intercurrent sickness up to the afternoon of his death.

NECROPSY

Examination was conducted 12 hours and 45 minutes after death. The body had been arterially embalmed within one and one-half hours after death. At the necropsy the gross findings were all essentially negative with the exception of the heart and lungs. The heart was found to be of about normal size for a man of this age, general stature and development. It weighed 308 grams and on external inspection was negative except for a moderate dilatation of all the cardiac chambers. There were about 100 c.c. of clear fluid in each pleural cavity and the lungs were strikingly edematous so that fluid ran freely from the cut section. Aside from a subendocardial hemorrhage in the left cardiac ventricle, small petechial hemorrhages in the gastric mucosa and a moderate atherosclerosis of the descending branch of the left coronary, no other findings of interest or importance were observed. The brain and spinal cord were negative.

Histologic Pathology. Fifteen different blocks were sectioned from various areas throughout the myocardium. The largest number were taken through the interventricular septum. In all sections extensive fragmentation and segmentation were present. Some hypertrophy of occasional fibers and some *lipomatosis destruens* were also present but the most striking feature of the reaction was the extensive fragmentation. Sometimes between these groups of fragmented and segmented fibers an edematous fluid was encountered made up of a pink staining albuminous precipitate. In some areas fat tissue had extended deeply into the myocardium. In one area an old hyaline scar was seen. Here the muscle fibers had been replaced by hyalinized, almost anuclear connective tissue. Of most importance were two foci of acute and chronic interstitial myocarditis, consisting in each instance of a small focus of infiltrating leukocytes which under the higher magnification were found to be chiefly lymphocytes although occasional plasma cells were also present. These foci of cells were separating the myocardial fibers and in one area the fibers had lost their nuclei.

Sections through the lungs, taken in different areas, showed a very high grade edema; the alveoli were filled with a homogeneous pink staining precipitate. Occasionally wandering polymorphonuclear leukocytes were found which had escaped into this fluid in the lumen of the alveolus. Occasionally also fibrin strands enmeshing polymorphonuclear leukocytes were seen in the alveoli. There was some infiltration of polymorphonuclear leukocytes beneath the mucosa of the bronchi and trachea. The mucosa itself was intact for the most part and the leukocytes were present both in the blood vessels and in the interstitial tissue. Round cells, plasma cells and interstitial edema were likewise seen in the submucous connective tissue beneath the bronchial epithelium.

The liver showed some fine pigment granules in the parenchymal cells about the central veins and there was some pigment phagocytosis of the cells of the splenic pulp.

The thyroid gland showed a definite overgrowth of the acinar epithelium. The cells were cuboid or columnar and the colloid pale and peripherally vacuolated. The gland grossly was but moderately enlarged. Otherwise, aside from a small congenital hemangioma of the liver and mild atherosclerosis of the descending branch of the left coronary artery, nothing of histological moment was encountered.

Case 3. A 13 year old boy entered the hospital for a foot operation. Complete physical and laboratory examination showed no variation from the normal except for the feet. The heart sounds and rate were normal and of good quality and the rhythm was regular. No murmurs were elicited. The lungs were clear and resonant. No râles were heard. The abdomen was negative. He underwent an operation for

rigid left foot and a flexed cleft foot on the right. Bilateral heel tendon lengthening and lengthening of the left perineals were carried out. He was under cyclopropane anesthesia for 1 hour and 35 minutes and left the table in excellent condition with a pulse rate of 74. Throughout the day he appeared to be having a normal recovery from his operation when suddenly at 11:15 p.m. of the day upon which the operation took place, his pulse became very rapid and when first counted was 150 per minute. He began to develop signs of pulmonary edema. The pulse became even more rapid and weak and signs of pulmonary consolidation, particularly on the right side, became striking. A diagnosis of possible pulmonary embolism was made. At 8 a.m. the following morning the temperature was 103° F. axillary and the respiratory rate was forty. Edema became more advanced and the patient expired at 1:55 p.m., 27 hours after his operation. No history of any previous cardiac disturbance was elicited from the family. The only information that was obtained was to the effect that the boy had never been robust and had always failed to take part in the more strenuous games with his associates.

NECROPSY

Examination was conducted 35 minutes after the patient expired. No embalming had been done. A moderate degree of cyanosis was present. No other findings on external examination were of importance. In the chest the heart showed wide dilatation of all its chambers. It weighed 175 grams. The muscle was flabby and the *columnae carnae* were flattened. The heart was opened in situ and the pulmonary artery was investigated for possible embolism but none was found. On the surface of the epicardium a very delicate, semi-granular exudate was visible suggesting a beginning pericarditis. About 50 c.c. of free fluid were found in both pleural cavities and the lungs were the seat of a very marked edema and advanced posterior congestion on both sides. In the dependent areas of both lungs, small hemorrhagic foci of semi-consolidation were seen on cross section which suggested a very early pneumonic infiltration. In the left axillary line region over an area measuring about 10 by 5 cm. healing, hyalinized tubercles and adhesions were present. The hilar lymph nodes were the seat of a fibro-caseous tuberculosis and multiple miliary healed subcapsular tubercles were found in the liver. There was a persistent thymus, a relatively small aorta and operative incisions on both feet. There was no evidence of pulmonary embolism, nor of thrombosis in the veins of the legs.

Histologic Pathology. Numerous sections were taken through the heart. In most instances the myocardial fibers showed some cloudy swellings and some separation of the fibers as well as a moderate degree of fragmentation and segmentation. None of these changes were particularly striking. However, in some areas there was a slight increase of connective tissue of a loose, edematous character about the blood vessels and occasionally the endothelial lining of these vessels was swollen and almost exfoliated. In some areas, particularly in the auricular muscle, there was wide separation of many of the fibers. Occasional small areas were seen where there were small scar foci about the blood vessels. One or two areas were found where there was an infiltration with polymorphonuclear leukocytes into subepicardial fat. Rare focal infiltrations of both round cells and polymorphonuclear leukocytes were found in the myocardium. These focal infiltrates were characteristic of an acute and chronic interstitial myocarditis. The muscle fibers in these focal areas were degenerated and fragmented and had lost their striations.

The lungs showed an early broncho-pneumonia superimposed upon a massive edema. The alveolar exudate was rich in pus cells and very little fibrin was present, although considerable serum and many red cells were found. Most of the pus cells were in an excellent stage of preservation. Healed hyalinized tubercles with a central area of caseation were found beneath the pleura. These tubercles were very numerous in the pleura but none were found in the lung parenchyma.

The liver showed caseous tubercles with a thick fibrous capsule about them. The liver cells showed only a mild degree of cloudy swelling and no passive congestion.

The spleen showed occasional miliary tubercles in the pulp. These tubercles were made up largely of masses of endothelioid cells without caseous centers. The sinusoids were quite prominent.

The other organs presented no noteworthy variation from the normal.

COMMENT

In the first case death was apparently almost instantaneous but the factor of electrical shock may have been a feature in the sudden cessation of heart action. In the second case, which like the first was of forensic as well as scientific interest, a careful analysis of the ingredients of the paint used showed that the only toxic substance in the paint was naphtha. It was considered that the inhalation of the paint was of no consequence in the heart failure inasmuch as there was no manifestation of naphtha intoxication found at the necropsy. The brief period of exposure to which the patient had been subjected to the fumes of naphtha and particularly the absence of symptoms in other workers confirmed this belief. Moreover, this man had worked in the open air for almost an hour after leaving the tank painting job and did not show any evidence of heart failure until he reached home. The symptoms of acute pulmonary edema were the only findings other than a rapid pulse that presented themselves throughout the short period he was alive after the onset of his cardiac failure. The only history of any possible previous cardiac damage was that obtained from a hospital admission record some 11 years prior to his death when a diagnosis of influenza was made and an occasional extrasystole was discovered on examining the chest. The possible relationship of a moderately toxic thyroid gland should be considered.

In the third case the symptoms of cardiac failure did not become clinically manifest until 12 hours after operation and these symptoms grew progressively more pronounced until the patient died some 15 hours after the onset of cardiac failure. Any possible relation of the prolonged cyclopropane anesthetic to the heart failure would be pure speculation. No evidence in the other viscera, such as the liver, showed any toxic change.

DISCUSSION

Acute interstitial myocarditis has been reported in infants and the aged but the majority of cases have occurred between the ages of 20 and 50. There have been no characteristic clinical findings in the cases which were studied over any period of time. As a rule the history has been that of rather rapid and progressive myocardial failure. The etiology is unknown, although infections, such as syphilis, rheumatic fever, influenza, gonorrhea, measles and remote infections and burns have been blamed. In many instances there was neither clinical evidence nor a past history of any infec-

tious process and careful bacteriological and histological studies of the myocardial lesions have not been successful in revealing any consistent etiological factor.

Interstitial myocarditis should receive serious consideration in any case of sudden and unexpected death where at necropsy the naked eye examination reveals no anatomic lesion which could be held responsible for the sudden exit. Moreover, it should be emphasized that it may require a very careful and sometimes painstaking microscopic study of the myocardium before this lesion can be found. In all three of the cases which we have just recorded a complete necropsy examination was conducted which in two instances included a careful study of the brain and spinal cord and the only possible cause of death was found only after careful search of many microscopic sections of the myocardium. A moderately dilated heart and pulmonary edema were the only gross findings which led us to conduct such searching histologic investigation.

Very little information has been obtained from electrocardiographic studies on those patients where these were undertaken. De la Chapelle and Graef⁵ observed "a prolonged PR interval, complete intraventricular block and low voltage in all leads with a normal sinus rhythm, while Scott and Saphir⁶ observed only a left ventricular preponderance."

Among the cases of sudden death from acute interstitial myocarditis, the following have been reported: In 1898 Freund⁷ observed a patient who had been suffering for many months with polyarthritis. This patient suddenly went into coma and died. In 1901 Zuppinger⁸ was treating a patient for infection in the groin. This patient was suddenly seized with cramps and died.

Saltykow⁹ in 1905 reported an instance where the subject, while undergoing treatment for burns, died suddenly. There were no visceral changes aside from those observed in the heart.

In 1921 Fiebach¹⁰ recorded an instance where a patient entered the hospital with acute cardiac failure and died the following day. In the same year von Gierke¹¹ reported a case of a 25 year old servant girl apparently in normal health who died suddenly while beating a carpet.

Lemke¹² in 1924 first saw his patient in acute cardiac failure and the same was true of Schminche's case.¹³

In 1929 Legrand and Nayrac¹⁴ reported a case of a patient 69 years old who died of rupture of the left ventricle four days after seeming to recover from a convulsion.

Thus, in a series of 52 reported instances of acute isolated interstitial myocarditis there were but eight cases that died unexpectedly and suddenly. Although quite rare when considered from the standpoint of the number of reported cases, nevertheless interstitial myocarditis does constitute a definite, important and perhaps not infrequently unrecognized cause of sudden death.

CONCLUSION

Three cases of acute interstitial myocarditis causing sudden and unexpected death are reported. In all instances a laborious microscopic examination of the myocardium was necessary before the lesion was found. The necessity for painstaking histologic investigation of the myocardium in sudden death is obvious.

Acute interstitial myocarditis may be the sole cause of sudden and unexpected death.

BIBLIOGRAPHY

1. SIMON, M. A., and WOLPAW, S.: Acute, subacute and chronic isolated myocarditis: report of a case, *Arch. Int. Med.*, 1935, lvi, 1136.
2. SCOTT, R. W., and SIMON, M. A.: Acute isolated (Fiedler's) myocarditis, *Trans. Assoc. Am. Phys.*, 1936, li, 374.
3. HIRAI, M.: Ein Fall acuter, idiopathischer interstitieller Myocarditis nach Appendicitis-Operation, *Trans. Soc. Path. Jap.*, 1936, xxvi, 79.
4. KJAERGAARD, H.: Acute myocarditis, *Acta med. Scand.*, 1936, lxxviii, 151.
5. DE LA CHAPELLE, C. E., and GRAEF, I.: Acute isolated myocarditis, with report of a case, *Arch. Int. Med.*, 1931, xlvii, 942.
6. SCOTT, R. W., and SAPHIR, O.: Acute isolated myocarditis, *Am. Heart Jr.*, 1929, v, 129.
7. FREUND: Zur Kenntnis der akuten diffusen Myokarditis, *Berl. klin. Wchnschr.*, 1898, xxv, 1077, 1106.
8. ZUPPINGER: *Wien. klin. Wchnschr.*, 1901, xiv, 799.
9. SALTYKOW, S.: Ueber diffuse Myokarditis, *Virchow's Arch. f. path. Anat. u. Physiol.*, 1905, clxxxii, 1.
10. FIEBACH, R.: Ueber isolierte diffuse akute interstitielle Myokarditis, *Virchow's Arch. f. path. Anat. u. Physiol.*, 1921, ccxxxiii, 57.
11. VON GIERKE, E.: Ueber granulierend-produktive Myocarditis mit Regeneration von Herzmuskelfasern, *Beitr. z. path. Anat. u. z. allg. Path.*, 1921, lxix, 72.
12. LEMKE, RUDOLF: Zur Frage der primären akuten und parenchymatösen Myokarditis, *Virchow's Arch. f. path. Anat. u. Physiol.*, 1924, ccxlviii, 345.
13. SCHMINCHE, M.: Demonstrationen zur Herz und Gefäßpathologie: Isolierte akute, diffuse, interstitielle Myokarditis bei einer 26 jährigen Frau, *Deutsche. med. Wchnschr.*, 1921, xlvii, 1047.
14. LEGRAND, R., and NAYRAC, P.: Mécanisme inhabituel d'une rupture cardiaque, *Compt. rend. Soc. de biol.*, 1929, c, 886.

THE INCIDENCE OF PNEUMOCOCCUS TYPES AND THE RELIABILITY OF THE NEUFELD TYPING METHOD *

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FOLLOWING the separation of Group IV pneumococci into 29 serologically distinct types by Cooper and her co-workers,¹ a fresh study of the type distribution of pneumococci in different localities has become necessary. Reports of such investigations have appeared from Boston,² New York,³ Cincinnati,⁴ and San Francisco.⁵ It is the purpose of the present paper to show the incidence of the various types of pneumococci in patients with pneumonia and also in other persons in the District of Columbia.

MATERIALS AND METHODS

All specimens of sputum examined in the Health Department Laboratory and in the Central Laboratory of the George Washington University Hospital, and found to contain pneumococci, are included in this study. Sputums were obtained from patients in the adult wards of Gallinger Municipal Hospital and other hospitals in the city, and from private patients, both at their homes and in hospitals. Accordingly, a fair cross-section of the adult population of the City of Washington is represented.

Typing by the Neufeld technic was performed at the beginning of the study by using only Types I, II, V, VII and VIII rabbit serum, but later tests were performed by this method for all types. In nearly every case (and in every case in which a type was not found by the Neufeld method), the Neufeld typing was followed by the injection of sputum into a white mouse. The peritoneal exudate and a culture from the heart's blood of the mouse were typed by macroscopic agglutination using horse serums for all types (kindly furnished by the late Miss Georgia Cooper). If the types found in a previous sputum or other specimen from the same patient corresponded with the type found by the Neufeld method, typing by the mouse method was usually not carried out.

For the Neufeld test we have used both the hanging-drop method originally described by Sabin,⁶ and also the method of placing the sputum-serum mixture flat on a slide under a cover-slip, as proposed by Beckler and MacLeod.⁷ Both methods have worked well. The latter method is the quickest and simplest. The hanging-drop method, on the other hand, has the advantage of not drying up when it is kept for several hours. Occasionally

* Received for publication October 11, 1938.

From the Health Department, District of Columbia, and the Department of Medicine, George Washington University School of Medicine.

we have obtained a "quellung" after this interval which did not appear earlier.

RESULTS

In table 1 are shown the results of sputum typing in 445 persons, composed of 302 cases of lobar pneumonia. Fifty cases of pneumonia of atypi-

TABLE I
Pneumococcus Types in Relation to Disease

TYPE	From Pneumonia						From Other Sources	
	Lobar Pneumonia		Atypical or Broncho-pneumonia		Total Pneumonias		Lung Abscess and Bronchitis	Carriers
	No.	%	No.	%	No.	%	No.	No.
I	86	29	2	4	88	25	0	1
II	14	5	0	0	14	4	0	0
III	23	8	8	16	31	9	2	4
IV	11	4	3	6	14	4	0	2
V	21	7	0	0	21	6	0	0
VI	9	3	3	6	12	3	1	4
VII	22	7	3	6	25	7	0	2
VIII	25	8	4	8	29	8	1	1
IX	4		5		9		0	4
X	6		2		8		0	11
XI	6		0		6		2	2
XII	9		1		10		1	2
XIII	4		2		6		0	2
XIV	6		1		7		0	3
XV	1		0		1		1	4
XVI	5		2		7		1	4
XVII	4		1		5		1	4
XVIII	5		1		6		1	2
XIX	10		0		10		0	6
XX	0		1		1		2	2
XXI	5		0		5		0	1
XXII	6		1		7		0	3
XXIII	2		1		3		0	2
XXIV	0		4		4		1	5
XXV	6		1		7		0	1
XXVII	3		1		4		0	1
XXVIII	2		2		4		0	1
XXIX	3		1		4		0	2
XXXI	3		0		3		0	2
XXXII	1		0		1		1	1
Total	302		50		352		15	79

cal distribution (often called bronchopneumonia), 15 cases of other lung infections in which pneumococci were presumably etiologically connected, and 79 cases in which there was no pneumococcal respiratory disease. The last group included patients who had tuberculosis, simple coryza, or a non-respiratory disease, or who were normal individuals.

Type I pneumococci were found in 29 per cent of the cases of lobar and 4 per cent of the cases of atypical pneumonia. Type II pneumococci caused 5 per cent of all lobar pneumonias and no bronchopneumonias. Types V, VII and VIII pneumococci accounted for 7, 7 and 8 per cent, respectively, of the lobar pneumonias, and 0, 6 and 8 per cent of the atypical pneumonias. In contrast to the foregoing types, Type III pneumococci were responsible for 8 per cent of the lobar pneumonias and 16 per cent of the atypical pneumonias. Pneumococci Types IV, VI and Types IX through XXXII were each responsible for a smaller percentage of the total cases of pneumonia, and were found to be associated with atypical pneumonia more often than were the lower types of pneumococci.

The types of pneumococci harbored by patients with no pneumococcal respiratory disease were usually Types III, IV, or VI pneumococci, or those belonging to the types beyond VIII. In general, the sputums of patients suffering from non-pneumonic infections (acute and chronic bronchitis and lung abscess) contained pneumococci of this same group.

Table 2 is a comparison of the incidence of pneumococci, Types I through VIII, found in patients with pneumonia in various large cities of the United

TABLE II
Incidence of Pneumococci in Various Cities

	Boston		New York		San Francisco		Cincinnati		Washington	
	1929-1936 (Finland)		1928-1936 (Bullowa et al.)		1932-1935 (Kohl & Reitzel)		1935-1937 (Benjamin et al.)		1935-1938 (Dowling & Abernethy)	
	No.	%	No.	%	No.	%	No.	%	No.	%
I	709	24.3	725	23.7	138	42.8	156	32.1	87	25.0
II	319	10.9	256	8.4	39	12.1	52	10.8	13	3.9
III	439	15.0	297	9.7	27	8.5	50	10.3	31	8.8
IV	65	2.2	179	5.8	3	0.9	20	4.3	14	4.0
V	226	7.7	230	7.5	11*	3.4	47	9.7	21	6.0
VI	61	2.1	51	1.7	2	0.6	9	1.9	12	3.4
VII	164	6.8	194	6.3	14	4.3	43	8.9	25	7.1
VIII	235	8.1	225	7.3	8	2.4	30	6.2	28	8.2
XIV	76	2.6	87	2.8	4	1.2	6	1.2	7	2.0

* Including Types IIa and V.

States. The incidence of these types in Washington was very similar to that occurring in the other cities in the east, except that the percentage of Type II pneumonias was lower in this series than in studies coming from

cities farther north. This low incidence of Type II pneumonias was noted for each of the three years covered by the Washington study. The similarity between the type distribution of pneumococci in the eastern cities and that found in Cincinnati in the middle-west and San Francisco on the west coast, while close, is not as exact. Perhaps if the three studies which involve smaller groups of cases could be extended to include one thousand or more, as in the reports from Boston and New York, the figures would coincide even more closely.

RELIABILITY OF THE NEUFELD TEST ON SPUTUM

The Incidence of Positive Neufeld Reactions. The Neufeld test was performed on a total of 305 specimens of sputum. As shown in table 3, in 161 cases the same type was found by both the Neufeld and the mouse methods; or, if more than one type was found by either method, the predominant organism was found by both methods, or the same two types were found by both methods.

TABLE III
Reliability of the Neufeld Method

	How Confirmed			Total
	By Another Sputum	By Other Sources of Material	Not Confirmed	
Neufeld and mouse methods agree in one or more types.	27	15	119	161
Neufeld negative; mouse positive.	12	3	65	80
Neufeld positive; mouse negative.	1	0	1	2
Neufeld positive; mouse not done.	14	4	43	61
Neufeld one type; mouse another type.	0	0	1	1
				<u>305</u>

In 80 instances, no type was obtained by the Neufeld method, while from the mouse one, two, or even three types were isolated. In two cases the Neufeld test revealed one type while no pneumococcus could be obtained from the mouse. In a single case the Neufeld test revealed one type (Type XIII), while a different type (Type XXVIII) was obtained from the mouse.

It will be seen, therefore, that among 244 specimens of sputum typed by the Neufeld method and followed up by mouse typing, in 161 cases (66.0 per cent) the Neufeld test was confirmed, in 80 cases (32.8 per cent) the mouse test revealed a type while the Neufeld test did not, in two cases (0.8 per cent) a type was obtained by the Neufeld test while the mouse revealed

none, and in only one case where both tests were positive (0.4 per cent) were they contradictory in that a different type was obtained from each test.

The Accuracy of the Neufeld Reaction. The Neufeld test resulted in the finding of one or more types of pneumococci in 161 cases in which it was confirmed (for one or more of those types) by the mouse test; in one case in which it was contradicted by the mouse test; and in 18 cases in which the mouse test was not done on the same sputum but in which previous or subsequent specimens of sputum or of other exudates had revealed the same type of pneumococcus. Accordingly, in 180 cases in which the Neufeld test was confirmed by another test, it was found to be correct in 179 cases and (presumably) erroneous in one case. This would indicate that we found the test to be 99.4 per cent accurate when positive.

DISCUSSION

The foregoing data show that in the District of Columbia the type distribution of pneumococci in carriers and in patients with pneumonia is quite similar to that found in other large cities from which reports have been published. The major discrepancy is the low incidence of pneumococcus Type II pneumonias. In this connection, it may be recalled that Type II pneumococci are the most typically pathogenic of all the pneumococci. They are the least often found in the throats of normal persons; they are sometimes responsible for epidemics of pneumonia⁸; they, in conjunction with Type I pneumonias, cause the classical picture of lobar pneumonia; and they are associated with as high a mortality as any other type. It is interesting to speculate as to whether this type might not be found in a decreasing portion of patients with pneumonia as one goes farther south. It is to be hoped that studies similar to the present one will soon be made in cities south of Washington.

In other respects the data in the present paper confirm previous findings elsewhere. Types I and II pneumococci have been shown to cause typical lobar pneumonia most frequently, less often atypical pneumonias. They are rarely found in the throats of normal persons and are practically never obtained from the sputum of patients suffering from bronchitis or lung abscess. Types III, IV and VI pneumococci and the Types above VIII offer a definite contrast. They seldom cause pneumonia with the typical clinical picture, whereas they are frequently found in the throats of normal persons and in the sputum of patients suffering from bronchitis and lung abscess. Pneumococci Types V, VII and VIII occupy a middle ground. They cause a higher percentage of bronchopneumonias than do Types I and II pneumococci, but not as high as do Types III, IV, VI and the "higher" types. Moreover, Types V, VII and VIII pneumococci are only slightly more often found in the throats of normal persons and in the discharges from bronchitides and lung abscesses than Types I and II pneumococci.

Specific serum therapy has been shown to be of value in the treatment of pneumonia caused by Types I, II, V, VII and VIII pneumococci. Its effect upon pneumonias caused by the other types of pneumococci remains to be proved. Now that rabbit serum is being made commercially available for the treatment of the pneumonias caused by all types of pneumococci, it is necessary for clinicians and public health officials in each community to know exactly how many cases of each type they may expect to find. According to the data presented here, at least 50 per cent of all pneumonias found in Washington can be treated by the use of specific serum.

SUMMARY

1. The incidence of pneumococcus types found in cases of pneumonia, non-pneumonic respiratory disease, and in normal persons in Washington, D. C., has been presented.

2. The greatest percentage of pneumonias was caused by the following types of pneumococci in descending order of frequency: Types I, III, VIII, VII, V, IV, II and VI. These pneumococci, with the exception of Types III, IV and VI were rarely found in non-pneumonic respiratory infections or in the throats of normal persons.

3. The percentages of the various types found correspond, on the whole, to those found in similar studies from other cities in the north, mid-west and far west, except for a local scarcity in the percentage of Type II pneumococci.

4. The Neufeld method of sputum typing was found to give positive results in about two-thirds of all specimens examined. In about one-third of all cases, injection of the sputum into a white mouse was necessary to determine the type of pneumococcus present.

5. Although less delicate than the mouse method, the Neufeld method was 99.4 per cent accurate, when positive, as compared with the mouse method.

The technical work for this study was performed by Miss Margaret C. McMahon, Mrs. Marie T. Woodwell and Miss Emily A. M. Godfrey.

BIBLIOGRAPHY

1. COOPER, G., EDWARDS, M., and ROSENSTEIN, C.: The separation of types among the pneumococci hitherto called Group IV and the development of therapeutic antisera for these types, *Jr. Exper. Med.*, 1929, xlix, 461-474.
- COOPER, G., ROSENSTEIN, C., WALTER, A., and PEIZER, L.: The further separation of types among the pneumococci hitherto included in group IV and the development of therapeutic antisera for these types, *Jr. Exper. Med.*, 1932, lv, 531-554.
2. FINLAND, M.: The significance of specific pneumococcus types in disease, including Types IV to XXXII (Cooper), *ANN. INT. MED.*, 1937, x, 1531-1541.
3. BULLOWA, J. G. M., and WILCOX, C.: Endemic pneumonia. Pneumococcic types and their variations in incidence and mortality for adults and children, *Arch. Int. Med.*, 1937, lix, 394-407.

4. BENJAMIN, J. E., BLANKENHORN, M., RUEGSEGGER, J. M., and SENIOR, F. A.: A study of the diagnosis and treatment of lobar pneumonia according to types and specific serum therapy, *ANN. INT. MED.*, 1937, xi, 437-447.
5. KOHL, C., and REITZEL, R. J.: Type specificity in pneumonia and pneumococcic infections, *Jr. Am. Med. Assoc.*, 1936, cvi, 1557-1561.
6. SABIN, A. B.: Immediate pneumococcus typing directly from sputum by the Neufeld reaction, *Jr. Am. Med. Assoc.*, 1933, c, 1584-1586.
7. BECKLER, E., and MACLEOD, P.: The Neufeld method of pneumococcus type determination as carried out in a public health laboratory: a study of 760 typings, *Jr. Clin. Invest.*, 1934, xiii, 901-907.
8. HARRIS, A. H., and INGRAHAM, H. S.: A study of the carrier condition associated with Type II pneumonia in a camp of the Civilian Conservation Corps, *Jr. Clin. Invest.*, 1937, xvi, 41-48.

TREATMENT OF HEART FAILURE *

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THE treatment of heart failure is too broad a subject to be comprehensively discussed in every detail in the brief space of one paper. It is manifestly necessary to touch upon much of the material in outline form and simply to state briefly the present status of the traditional forms of therapy. Newer methods and drugs that seem to be particularly interesting and promising will be more extensively commented upon. Personal observations or confirmations of the observations of others that seem particularly significant will be set forth. A report of some original or corroborative studies must be included in order to warrant publication. This will consist of a summary of work done during the past several years with the help of many associates, but particularly that of Dr. George M. Decherd, Jr.

The delineation of personally directed investigations is reserved for the body and the end of the paper, and may perhaps thus receive undue emphasis. The studies of the chemical nature of heart failure have been discussed in a previous communication.¹ The therapeutic approaches suggested by this work have not yet advanced to a point where they rate more than being mentioned in a conservative paper. Our conclusions as to the mechanisms by which the two main types of diuretics, the xanthines and the mercurials, accomplish their results will be presented. Observations on the newer and better combinations of drugs for the elimination of edema fluids will, however, be reported upon somewhat more in detail.

PREVENTIVE THERAPY

The treatment of heart failure should be taken into consideration upon the discovery of evidences of potential heart disease or myocardial damage. The pronouncement of the diagnosis is best withheld. Steps, however, should be taken immediately to work out a plan of life that will protect asymptomatic cardiac patients. The hope is to postpone as long as possible the almost inevitable heart failure. The damaged heart, if spared every unnecessary strain, may carry on for years.

The removal of the *etiological factor* even when it is apparent is only rarely possible. Treatment directed against the causative process is nevertheless in order in the hope that the progress of the condition may be arrested. Chronic syphilis should be treated most carefully and persistently in the presence of syphilitic aortic disease. The milder antisyphilitic drugs should be continued for long periods of time. Bismuth, mercury and

* Read at the St. Louis meeting of the American College of Physicians, April 17, 1937.
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iodides if administered year in and year out will accomplish almost as much as neoarsphenamine and are much less dangerous.

Rheumatic fever is almost an unknown quantity bacteriologically. Rest in bed for many months is justified treatment. The use of daily rations of salicylates if well tolerated for as long as two years after an acute attack has only empirical support. The removal of infected tonsils is of disputed value.

Hyperthyroidism, of course, may be controlled by medical and surgical means and the cardiac damage may be prevented although the original condition is not amenable to prophylaxis.

The hypertensive arterial cardiorenal disorders are usually insidious in their onset and well developed when discovered. Many factors in the genesis, pathological physiology and progress of hyperpiesia are fairly well understood. There is no certain method for permanently lowering blood pressure to normal levels. Management, however, may accomplish much in prevention or in checking the speed of progress of the degenerative changes. A moderately low protein, low fat, salt poor, high calcium and high vitamin diet may contribute to some extent toward this end. Such dietary restrictions are indispensable in patients with chronic nephritis. The stemming of the tide in these disorders and in premature degenerative arterial disease are the problems of modern preventive medicine.

SOME FUNDAMENTAL PATHOPHYSIOLOGICAL CONSIDERATIONS

Inasmuch as the causative factors of heart disease are still for the most part beyond control, we must concentrate our efforts on the control of those *precipitating factors* that lead toward or are important in the development of heart failure. Over-exertion must be avoided. Acute and chronic infections and increased metabolic rate are generally recognized as factors which would contribute to further cardiac damage and call for careful management. Unfortunately little can be done to prevent the sudden or slow development of obstructive lesions in the coronary system, or cardiac hypertrophy and enlargement. The advance of sclerosis of the coronary bed and increase of cardiac hypertrophy are progressive processes which go on insidiously, but may be significantly slowed by proper management. Chronic myocardial anoxemia would account for the chemical abnormalities that have been noted in the hearts of patients who have died of heart failure.¹ Hypertrophy of heart muscle cells undoubtedly interferes with the circulation and impairs the oxygenation and nutrition of the cells.² Oxygen administration may be of considerable help.

EXPERIMENTAL ATTEMPTS AT PHYSIOLOGICAL ADJUSTMENTS

Consideration of the chemical changes such as have been outlined in the previous papers¹ should aid in the understanding of the nature of the degenerative processes that are going on silently as the heart disease progresses.

The further investigation and absolute definition of these changes eventually may contribute something more in the way of a rational myocardial protective therapeutic regime. The electrolyte changes in the blood stream and the blood serum protein losses¹ and chemical changes in the tissues are apparently not of first importance. The phosphocreatine disturbances in the heart muscle are of the greatest significance. Measures that would tend to conserve phosphocreatine, total creatine and phosphorus would tend to postpone the evil day of heart failure.

Aminoacids as alanine, glycocoll and glycoamine and arginine have been suggested to stem the loss of creatine and of phosphorus and presumably of phosphocreatine in the heart muscle. The suggestions have come from theoretical considerations and from perfusion experiments with solutions containing the specific substances. Our own experiments were not as successful as those of the Englishmen at Oxford. We have found, however, that the amino-acid glycocoll administered by mouth in one gram doses, even in the presence of extreme heart failure, will often relieve the sense of exhaustion that such patients experience and tide the patient over a crisis. Glycocoll seems to act beneficially even after coronary thrombosis with extensive myocardial infarction. This has not yet been conclusively demonstrated to be anything more than a specific dynamic effect of the aminoacids. Glycocoll cannot, therefore, as yet be recommended for general use.

Digitalis in adequate dosage as shown by our experimental studies¹² and some clinical studies, has a tendency to conserve and apparently in some instances to increase the total creatinine content of the heart muscle.³ Furthermore, the animals whose hearts have been put under the stress of traumatic valvular lesions and digitalized live longer and develop less cardiac enlargement.¹⁴ Digitalized rabbits subjected to sudden myocardial stretching from injections of volumes of 6 per cent or 12 per cent buffered acacia solution equal to the blood volume of the animal had a much lower mortality rate and developed on the average statistically lesser grades of hypertrophy.¹ Our hypertrophy limiting results with digitalization have not, however, been nearly so striking as those of Cloetta³ upon the basis of which Christian⁴ recommended the regular use of digitalis to limit cardiac hypertrophy. We have added the suggestive chemical evidence of the possible beneficial creatine-conserving action of digitalis.¹⁰ There may be some question raised as to the validity of the established basis for the routine administration of digitalis as a prophylactic against advancing hypertrophy and failure in patients with potential or probable asymptomatic heart disease. Nevertheless, further clinical observations of the effect of years of digitalization seem to be in order.

INCREASING THE OXYGENATION OF THE HEART MUSCLE

Oxygen is evidently the most essential element, the curtailment of which is most threatening to the maintenance of adequate heart muscle

function.⁵ Unfortunately we are not able with ease to bring oxygen directly to the heart muscle cells. Indirectly we have long used the xanthines, particularly aminophylline, with the hope that coronary vasodilatation and consequently better myocardial oxygenation would be accomplished. An augmentation of the deficient blood supply to a heart should contribute to more nearly normal oxygenation and more adequate metabolism and would account for observed clinical improvement. The question has been raised as to whether the xanthines really act as they have been thought to act, as vasodilators. Recent careful perfusion experiments have failed to show any increase in coronary flow in the isolated heart after the use of xanthines. Gold and his coworkers⁶ have failed to obtain clinical evidence of any beneficial effect of xanthines in angina pectoris. These conclusions are contrary to the earlier findings of Fred Smith and the results of Friedman, Resnik, Calhoun and Harrison.⁵

I still believe that something more than psychotherapeutic results is obtained with xanthines if the dosage is adequate. The report that aminophylline was ineffectual has, however, cast some doubt upon the logic of its daily use in asymptomatic heart disease as well as in those with symptoms of coronary or myocardial insufficiency. The Council on Pharmacy and Chemistry of the American Medical Association now accepts xanthines as diuretics and myocardial stimulants but not as vasodilators.

GENERAL CONSIDERATIONS

Treatment, after the appearance of symptoms of heart failure, depends upon the type of heart failure. The treatment of the anginal type of heart failure will not be further discussed.

In the milder forms of congestive failure, the patient may present nothing more than easy fatigability, weakness and physical exhaustion, without or with increasing breathlessness. The indications are for the temporary alleviation of the physical and consequently the circulatory load, with a definite decrease in the demand for oxygen or for a *lowering of the basal metabolism*. Small frequent feedings of a well balanced diet, low in fats, high in vitamins, gelatin, and carbohydrates, unless there is diabetes mellitus, and adequate in proteins of good biological character is essential in an attempt to maintain osmotic pressures and homeostasis.

The minimal demands upon the heart muscle under a low basal metabolic status may be attained by subjecting the patient to partial *starvation* at *rest* in bed. Semistarvation and restriction of fluid and salt intake, and of physical activity to the limits established by careful observation of the patient's reaction, may be sufficient to keep borderline patients in circulatory equilibrium for long periods of time. The dietetic and physical management is usually supplemented by drug therapy in the form of small daily doses of digitalis or large doses of a xanthine preparation.

The patient is instructed *to avoid sudden stresses and strains*, to lower his body weight to somewhat below his standard weight and maintain it at that level; and to respect respiratory infections. Usually sooner or later as age advances, in spite of faithful abidance by restriction, trouble begins. Breathlessness comes on even with restricted activity. Periods of complete mental and physical rest, digitalization and sometimes the use of diuretics are necessary.

EMERGENCY THERAPY

Emergency measures are demanded in *acute congestive failure*. In *acute engorgement*, venesection or other methods of blood letting may be necessary to save life. The presence of a *serious cardiac mechanism disorder*, a paroxysmal auricular fibrillation or flutter, tachycardia, bradycardia or heart block which has precipitated or contributed to congestive failure calls for immediate specific measures for the control of the disorder.

The anoxemia of acute pulmonary edema or of pulmonary embolism or of coronary thrombosis calls for forced concentrated *oxygen* atmosphere to tide the patient through the crisis. Collections of transudated edema fluid in the body cavities, or even in the pericardium itself, acting as a handicap to the efficiency of respiration or to the movement of the diaphragm, or tamponading the heart, should be removed.

The *chronic type of heart failure* is by far the more common condition and requires the most persistent efforts and careful general management. An attitude of hopefulness and optimism is necessary in the handling of these conditions. In my experience there has been abundant justification for this psychotherapeutic measure. Many patients who have suffered from failure have been relieved of the distressing symptoms, made comfortable, happy and useful and practically rehabilitated by adequate treatment and judicious advice. The physician must be equipped and ready to change his methods and his therapeutic agents and to employ other preparations when the effects of those that he is using are no longer satisfactory.

SOME DETAILS OF ROUTINE MANAGEMENT

The potential or probable and asymptomatic heart disease patient should be given some protective and general dietary supervision.

Rest is perhaps the most important single therapeutic measure that can be instituted for the relief of the patient with the failing heart and circulatory embarrassment. Rest, however, to be effective must be complete, mental and physical, and must be prolonged. No detail that will contribute to the patient's comfort should be omitted. He should be supported in Fowler's position with a rather firm back rest and hard pillows. When possible a cardiac table as well as a cardiac bed should be provided. Evacuation of the bowels should be accomplished without any strain, preferably with the use of a bedpan slipped passively under the patient. If this is a

great ordeal for the patient it is sometimes less exhausting to have a commode, built to the level of the bed, upon which the patient may be gently lifted or shifted, without any effort on his part. It must be remembered that the lifting of the body weight even by the musculature of the arms is a considerable physical exertion. Changing of position in the bed should be done by the nurse and the patient spared every effort.

In the most severe stages of heart failure when a patient is dyspneic and orthopneic it is highly desirable to ensure rest by the use of sedatives. Paullin⁷ has recently called attention to the fact that morphine sulphate given hypodermically in $\frac{1}{4}$ to $\frac{1}{2}$ grain doses is one of the most valuable drugs used in the treatment of heart failure. As Houston⁸ has suggested, the sedative effect of morphine upon the respiratory center spares the patient the great muscular exertion of the usual overactivity of the respiratory mechanism in congestive failure. Morphine breaks the vicious circle that exhausts the patient, allays anxiety, relieves the strain and pain and ensures sleep. Dilaudid probably has some advantages over morphine sulphate in the prolonged treatment of cardiac invalids. It is apparently equally effective in the control of respiratory distress in considerably smaller dosage, namely $\frac{1}{64}$ to $\frac{1}{32}$ of a grain (1 to 2 mg.). The effect on the respiratory center as revealed by the rate must be carefully noted for in an occasional susceptible individual, a temporary suspension of breathing may occur and requires artificial respiration. The chief argument in favor of dilaudid, however, is the fact that it is not constipating, and that its withdrawal is not disturbing to the patient.

Diet. In general, in the presence of heart failure there should be some restriction in the total food taken each day and at each meal. There should be no large meal, but five or six small feedings so spaced as to allay hunger. At the same time, spread the work of digestion over periods of hours. The amount of fluid taken with each meal should be reduced to a minimum and taken slowly. Overfilling of the stomach and consequent mechanical embarrassment of the heart action is to be avoided.

A fairly balanced diet with a total caloric value between 1,200 and 1,500 made up of foods that have a tendency to yield an acid ash is most desirable. Sodium chloride should not be added to the food. The fluid intake for 24 hours should be limited to six glasses or 1,400 c.c.

The foods selected should be easily digestible dairy products, particularly milk and eggs. In the absence of diabetic tendencies carbohydrates with a high sugar content seem to be desirable.

One must not neglect the need for proteins of good biological character. Delicate meats, as chicken and fish and liver, milk and egg albumin in sufficient quantity must be supplied to meet the metabolic demands and in an attempt to maintain the blood proteins at a normal level. In one of my earlier chemical studies^{1b} I demonstrated the tendency toward abnormally low serum protein levels in patients with heart failure. Proteins are also

useful in furnishing urea and mineral electrolytes and in promoting optimal urinary secretion.

THE TREATMENT OF EDEMA

In the presence of extensive and refractory edema due to congestive failure, as nearly a salt free dietary as possible is necessary; and a flow fluid intake will also usually help to restore a normal water metabolism. The Karrell diet of four glasses of milk of 200 c.c. each, one every four hours and nothing else, is quite poorly balanced and inadequate and should be continued only for a few days to a week at the most. Carbohydrate and protein should be gradually added. This régime is usually sufficient to inaugurate a diuresis and once started it may continue. Other measures may be used to contribute to the maintenance of the diuresis.

High potassium containing foods as potatoes and bananas may be substituted for the milk. Later on the continental diet of unpeeled raw fruit and vegetables with only the natural juices for fluids, a total of 1,500 gm., may be tried. Skimmed milk, eggs and cereals must eventually be added to balance the diet. Any foods that cause distention or foods to which the patient has reacted abnormally should be eliminated from the diet.

Acid Salts. The administration of acid salts, as ammonium nitrate, ammonium chloride, potassium chloride or calcium chloride in doses of 15 to 30 gr. (1 to 2 gm.) three times a day may produce a relative acidosis and inaugurate or continue diuresis. Barker and his group⁹ in Chicago have reported good results from the use of potassium in effecting the replacement of sodium. I use acid salts, ammonium and potassium chloride, usually in conjunction with other diuretics, particularly the organic mercurials, to augment the effect of these preparations as Keith and his collaborators¹⁰ advocated. The shift in the sodium and chloride ion relationship in the relatively acidotic state and the decrease in the alkaline reserve and the increase in the permeability of the capillary walls and in the osmotic pressure of the blood plasma all favor the drawing of the fluids from the tissues. Ammonia is changed to urea leaving the chloride ion to combine with the fixed bases of the plasma and tissues.

Urea, itself, may be administered in doses as large as ($\frac{1}{2}$ to 1 ounce) 10 to 30 gm. a day if there is no evidence of impairment of renal function or retention of nitrogen waste products and this may be very effective in controlling the chronic types of dropsical states.

The antiquated saline catharsis method or a modification of it, consisting in the use of concentrated salts for the removal of fluid in the body, has been found to be far too drastic and has fallen into disrepute. Hypertonic enemas are no longer in use; in fact they are no longer considered to be innocuous. Mineral oil and agar agar emulsion with or without cascara to encourage regular bowel movements and make unnecessary any straining at the stool must be a part of the sane management in such cases.

Digitalis. Digitalis is the drug of choice in patients with heart disease. It is a cardiac tonic that relieves breathlessness and edema. It acts most dramatically in patients with auricular fibrillation. However, most edemas of congestive heart failure disappear under adequate digitalization whether the cardiac mechanism is regular or irregular, as Christian demonstrated many years ago.¹¹ There is now abundant evidence that digitalis acts primarily on the heart muscle in such cases. Dock and Tainter^{11a} have shown that there is a secondary but also important action of the drug upon the peripheral circulation.

In the presence of auricular fibrillation, digitalization, through vagus stimulation, depresses the conduction and decreases sharply the ventricular rate and eliminates the pulsus deficit. Occasionally the circus mechanism may stop spontaneously as a result of the improvement of the circulatory equilibrium and in spite of the myocardial blocking effects of digitalis. Digitalization improves considerably the general circulation, particularly that in the brain. Cheyne-Stokes breathing and paroxysmal nocturnal dyspnea may be entirely relieved. Similar results may be obtained by morphine or by the intravenous use of aminophylline which apparently favorably effects the cerebral circulation and the respiratory center as Nathanson has so clearly shown. Most patients require 1 cat unit per 4 kg. or for each 10 pounds of body weight for digitalization. This may be accomplished with the standard powdered leaf of digitalis, pills, capsules or the tincture. Using the rapid oral method I give 4 pills (6 gr.) or 4 cat units every 4 hours for two doses, then 4 pills every 6 hours for two doses, then one pill every 6 hours to nausea, vomiting, diarrhea, xanthophobia or block. The slower, and slightly safer method is to use 2 pills (3 gr.) every 4 hours for 10 doses, then one pill every 6 hours until symptoms appear. New digitalis preparations are appearing on the market and demand careful clinical assay.

More highly concentrated purified crystalline and amorphous preparations of digitalis glucosides have been introduced from time to time. These are described in the booklet, "The Cardiac Glucosides" by Arthur Stoll. The extensive bibliography of this book should be consulted for references that follow. In 1869, Nativelle described "digitaline cristallisée" as a crystalline insoluble very active principle of digitalis. This was probably digitoxin. It was not introduced until the pharmacologic work of Cloetta in 1920, which established the dose of 0.1 mg. (1/600 gr.) as equal to 0.1 gm. (1½ gr.) of the standard powdered leaf or 1 c.c. of the standard tincture of digitalis.

The gitalin fraction or amorphous gitalin isolated by Kraft and studied by Straub, introduced as verodigen and now called gitalin amorphous, is a highly purified cardiac glucoside isolated from digitalis purpurea. It is apparently rapidly and completely absorbed in the gastrointestinal tract. 0.25 mg., 1/240 grain, produces about the same clinical effect as 1½ grains of powdered leaf digitalis. The clinical dose necessary is small and has

therapeutically the desirable action of digitalis. The optimal effect is accomplished by 2.5 mg., 1/16 to 1/10 of a grain in a period of five to six days. Gitalin amorphous apparently retains its action without any change in potency or deterioration over periods as long as two years, according to Stroud and his co-workers.

Southeastern European, Balkan or Austrian *digitalis lanata* has yielded a number of very cardiac glycosides, according to German, French, Swiss, and English pharmacologists. S. Smith not only isolated digitoxin and gitoxin from *digitalis lanata* but also a new crystalline glucoside *digoxin* which cannot be obtained from *digitalis purpurea*. Digoxin was found to be a stable crystalline substance of known definite chemical composition

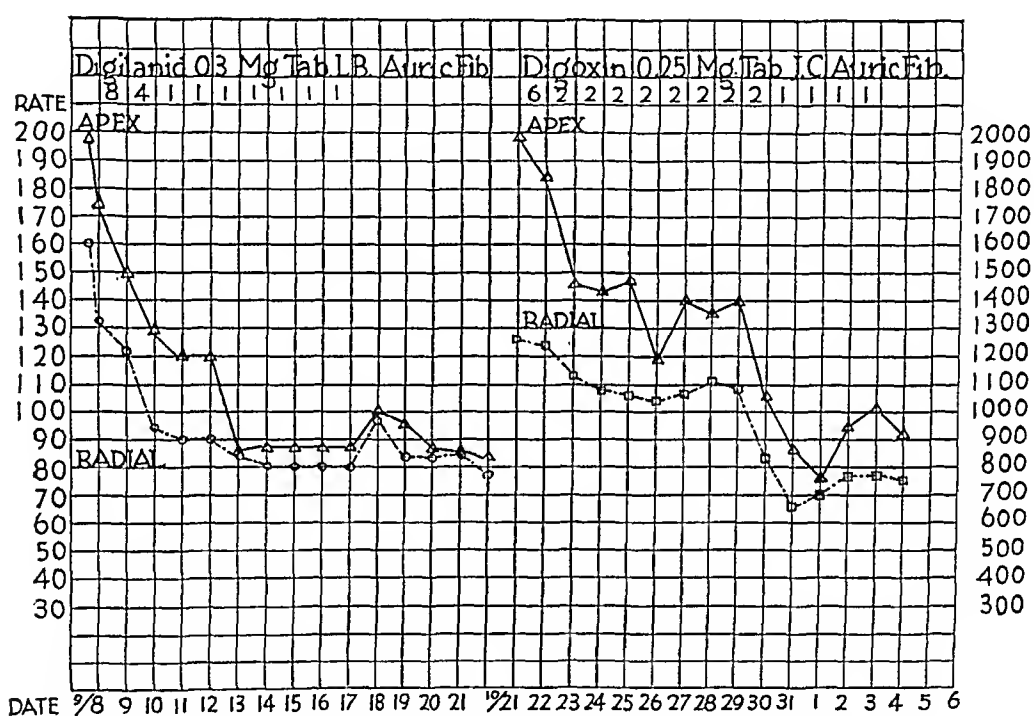


FIG. 1. Effects of digilanid and digoxin given by mouth on the heart and the pulse rates in a patient with auricular fibrillation.

($C_{41}H_{64}O_{14}$). Digoxin administered clinically was found to be effective even in very small doses of 0.25 mg. (1.240 grain) equal to 0.1 gm. (1.5 gr.) of powdered leaf digitalis. It is promptly and fairly completely absorbed. Digitalization can be accomplished with 1 to 1.5 mg. (1/60 to 1/40 grains). Intravenously the dose of 0.75 mg. to 1 mg. seems sufficient. Digoxin is very rapidly eliminated from the body and therefore the daily dosage of 1/3 the digitalizing dose, namely 0.5 mg. (1/120 grain), is necessary to maintain a digitalizing effect. The response to the intravenous dose of digoxin is evident within an hour and usually complete within two hours, but by mouth it takes about two hours before the effect is very definitely demonstrable and four hours before completion. The value of

the digoxin in terms of cat units is considered unnecessary by the manufacturers, since it is a chemical entity, the dosage of which can be accurately controlled by weighing. They argue, probably justly, that weighed digoxin is far more uniform than a preparation standardized by the cat method of assaying. Nevertheless, the cat unit value should be established and stated on every product, in order to prevent poisonings in the hands of some who are accustomed to considering one tablet of a cardiac glucoside to be equivalent of $1\frac{1}{2}$ gr. of the standard powdered leaf of *digitalis*, or one cat unit, as is so often the case with most other *digitalis* tablets.

Lewis ^{12a} has accepted digoxin in the place of the more variable and less safe strophanthin G. or ouabaine. Wayne ^{12b} reported favorably on the clinical efficiency of digoxin. Stroud's ^{12c} results with digoxin have been corroborative and my own limited experiences have been similar.

Digilanid glucosides extracted by Stoll and Kreis from the *digitalis lanata* were found by them to consist of isomorphic crystalline complexes made up of three chemically distinct substances. Lanata glucosides lanatids, or digilanids A, B and C, were found to make up A 47 per cent, B 17 per cent and C 36 per cent of the isomorphic crystalline complex respectively. By careful chemical analysis, hydrolysis and deacylation, Stoll and Kreis found digilanids A and B to yield identical substances to *purpurea* glucosides A and B. *Purpurea digitalis*, however, did not contain anything comparable to the important and most active digilanid C and its derivative digoxin. The isomorphic crystalline complex was found to be chemically pure and stable, insuring a constant relation between the therapeutic and toxic effect. Rapid absorption and prompt action, but particularly the persistence of its effect, are advantages in favor of this preparation. The amount of digilanid required for digitalization is about 1.0 mg. ($\frac{1}{60}$ grain), each tablet of $\frac{2}{3}$ mg. ($\frac{1}{100}$ grain) being equivalent to 1.0 gm. ($1\frac{1}{2}$ grains) of the standard powdered leaf or one cat unit. We have had good results from this preparation. The maintenance dose is $1\frac{1}{3}$ mg. or $\frac{1}{50}$ grain per day.

Digoxin and digilanid have been found to be so promptly, uniformly and completely effective that they have practically displaced other intravenous preparations. In auricular fibrillation they cause dramatic slowing of the ventricular action. These preparations also produce profuse diuresis in patients with edema just as the other *digitalis* preparations in adequate dosage are known to do.

In view of the creatine-conserving effect and possible hypertrophy-restraining action of *digitalis*, the question of whether prolonged digitalization in maintenance doses over periods of years produces any undesirable toxic changes in the heart must be opened again for debate. Bauer and Fromberg, using excessive doses of *digitalis*, apparently produced irreversible histological myocardial damage. Trendelenburg showed that the Starling heart-lung preparation responded to *digitalis* only after the myocardium had been overwhelmed. Edens has insisted that only the hypertrophic and failing heart responds to therapeutic doses of *digitalis* in characteristic

fashion. Experimentally, hypertrophied hearts were found by Weese to be increasingly sensitive to digitalis.

The heart muscle, especially when damaged, has a specific affinity for glucosides, and absorbs proportionately large amounts of these substances. Fixation of the glucosides in the heart muscle is responsible for the cumulative effect of digitalis administration. This is desirable and reversible when accomplished by small doses. The effect of digitoxin and digoxin may be considered irreversible, but continued irrigation will usually revive

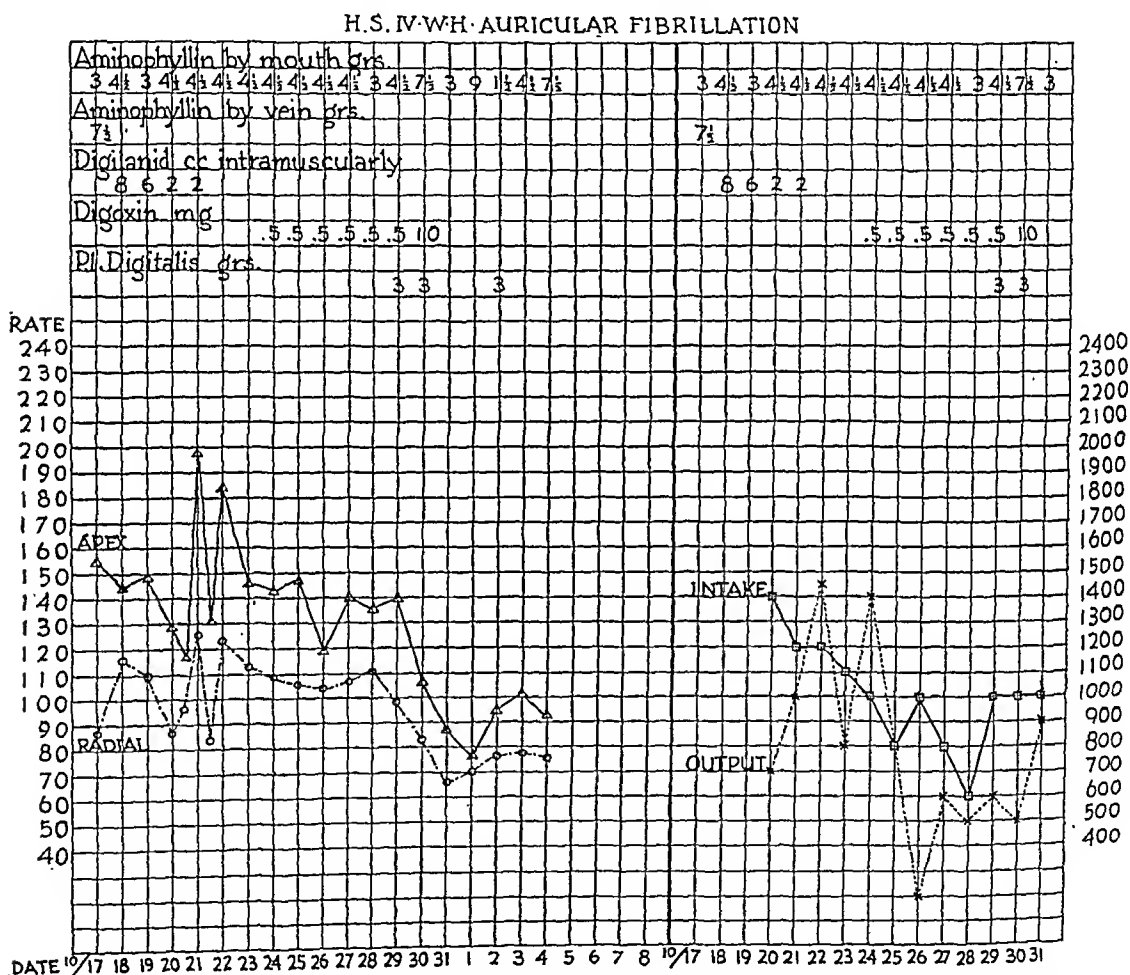


FIG. 2. Effects of digilanid and of digoxin on heart and pulse rate and fluid output in a patient with auricular fibrillation in chronic congestive heart failure and edema.

hearts, even when they have been stopped by such powerful glucosides. Digilanid C effect is more easily reversed. Digilanid B, Scillaren A, Strophanthin G, and gitoxin are most easily washed out.

Our clinical and experimental studies seemed to show a tendency to retention of creatine as the result of digitalization, which would be interpreted as a desirable effect. Our experimental studies have also revealed a tendency to restriction of hypertrophy by digitalization. We are beginning

to feel that perhaps there may be justification for the prolonged use of digitalis for this purpose.

The myocardial creatine-sparing value of digitalis noted in our experiments may be an argument for reconsidering the question of digitalization in pneumonia. The low levels of creatine in the heart muscle of those patients who had died of heart failure, but particularly those who had died of pneumonias, are a basis for reopening this discussion. The use of digitalis in pneumonia at the present time is unceremoniously condemned on statistically questionable grounds.

The Xanthines or Purines. Caffeine, theobromine and theophylline, members of the vegetable purine or xanthine group of diuretics, for some time past, have been widely used in the treatment of congestive heart failure. The theobromine and theophylline combinations have been accepted, up until recently, as effective in anginal failure. Caffeine, because of its cerebral stimulating effect is not routinely used in the treatment of chronic cardiac patients but is occasionally administered in the form of caffeine sodium benzoate as a temporary circulatory stimulant.

Theobromine preparations, particularly theobromine sodium salicylate "Diuretin," was one of the first of this group to be introduced as a renal diuretic in patients with edema. It is still quite widely used, particularly in combination with calcium to enhance its diuretic properties, or with a barbiturate as a sedative.

Theophylline derivatives, "Theocin," theophylline sodium salicylate, or calcium salicylate, theophylline with ethylene diamine, or with methyl glucamine have been, perhaps, most widely used as coronary vaso-dilator cardiac stimulant and diuretic agents. Smith⁵ and his coworkers found theophylline to be more effective than any other xanthine in increasing the coronary flow in the experimentally isolated heart. Confirmatory clinical evidence of the value of these drugs was brought forth by Friedman, Resnik, Calhoun and Harrison⁵ in a study of cardiac output and vital capacity of patients following treatment orally with theophylline salts, particularly aminophylline.

Aminophylline by mouth often greatly relieves paroxysmal dyspnea and sometimes causes attacks to disappear entirely for a time. I have found it worthwhile to use aminophylline in this way before resorting to its use intravenously or to digitalization or routine injections of morphine. Theophylline apparently produces myocardial stimulation, probably an increased coronary and cerebral blood flow and the removal of minimal amounts of edema. Latent edema, even though not demonstrable, may be significant.

In all of our original diuretic experiments in which we studied the effect of xanthines one day and of the mercurials the next day in the same patients it was frequently noted that there was a very definite augmentation of diuresis. We, therefore, tried various combinations of theophylline and mercurials and found that we could use much smaller doses of the mercurials and found that 1 c.c. of 10 per cent solution of salyrgan was as effective as 2 c.c. intravenously if we added 0.26 gm. (4 grains) of aminophylline. The

combination seemed to be less irritating and less toxic as well as more efficient. A mixture of a xanthine and a mercurial seemed to be rational. The supplementary actions of the two were totally different in effect and resulted in a definite increase of the urinary flow.

Our studies utilizing the creatinine clearances of Rehberg following the intravenous use of theophylline in patients with anasarca or generalized edema of congestive heart failure seemed to show that the theophylline accomplishes its diuresis primarily by increasing the glomerular filtration and affecting the reabsorption only slightly in the way of depression. The glomerular filtration may be considered as evidence of the vasodilation and

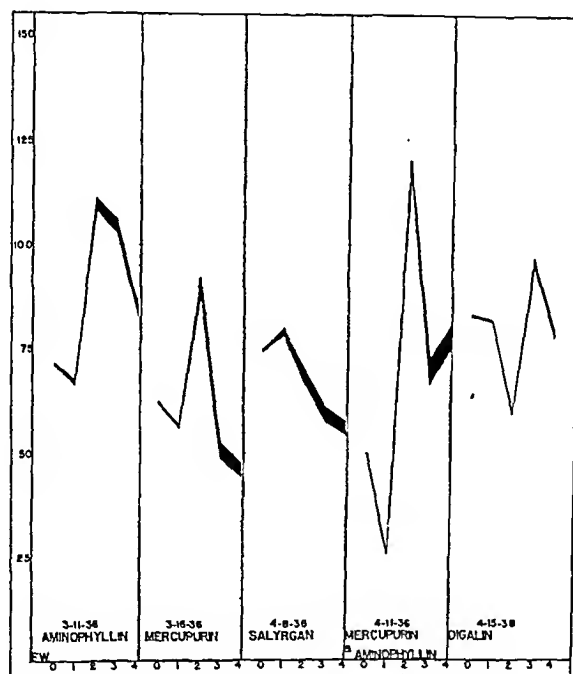


FIG. 3. Representation of glomerular filtration (upper edge) and tubular reabsorption (lower edge) as determined by creatinine clearance studies after various intravenous injections. Note the increased filtration with the xanthines and decreased reabsorption with the mercurials and combination effects.

increased blood flow to the kidneys. Edema interferes with adequate circulation and efficient oxygenation of water-logged tissue as well as adding a further burden of increased body weight. It is therefore desirable to remove edema as promptly as possible.

Mercurial Diuretics. Organic mercurial salts were introduced at first for intravenous use in the treatment of syphilis. Novasurol, one of the first of these preparations to be used with clinical benefit, was noted upon injection into patients with syphilitic aortic insufficiency and congestive failure to produce profound diuresis. Novasurol, however, was found to cause undesired reactions in certain individuals and less toxic organic mercurial salts were therefore sought. Merbaphen, mersalyl or salyrgan was introduced

and found to be much less toxic than the original preparation and just as efficient. In our creatinine clearance studies on the effect following the intravenous injection of salyrgan into patients with congestive heart failure and edema, we found that in contrast to theophylline the mercurials produced a marked decrease in tubular reabsorption and thereby accomplished the dramatic outpouring of edema fluids.

We have since learned that Foldy in experimenting with various new organic mercurial salts added a small amount of acid theophylline solution in order to neutralize the irritating alkalinity of new highly acid organic

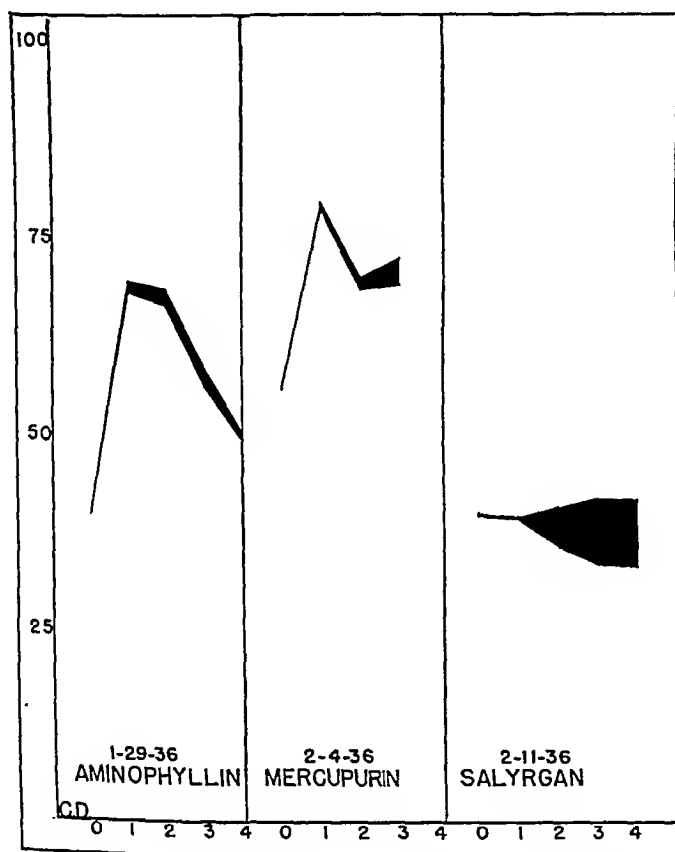


FIG. 4. Representation of glomerular filtration (upper edge) and tubular reabsorption (lower edge) as determined by creatinine clearance studies after various intravenous injections. Note the increased filtration with the xanthines and decreased reabsorption with the mercurials and combination effects.

sodium salt of mercury. The addition of the theophylline was found not only to make the combination non-irritating but also definitely to augment the action of the mercurial as diuretic in experimental animals.

A combination organic mercurial and theophylline diuretic under the trade name Novurit was put to clinical trial abroad as Novurit and was enthusiastically championed in the Hungarian publications of v. Issekutz and v. Vegh.¹⁵ It was introduced in this country as mercupurin, described as a sodium salt of trimethylcyclopentane-dicarboxylic acid-methoxy-mercury-

allylamide-theophylline, containing theophylline 3.5 per cent combined and 1.5 per cent free, making a total of 21.5 per cent of mercury. DeGraff, Nadler and Batterman¹⁶ who have studied the preparation extensively have stated that the 13.5 per cent aqueous solution of mercupurin contained 29.1 per cent of mercury by weight so that 1 c.c. contained 0.0393 gram of mercury, comparing thus favorably with salyrgan containing 39.5 per cent mercury by weight and 1 c.c. of the same 10 per cent solution containing 0.0396 gm. of mercury about the same amount.

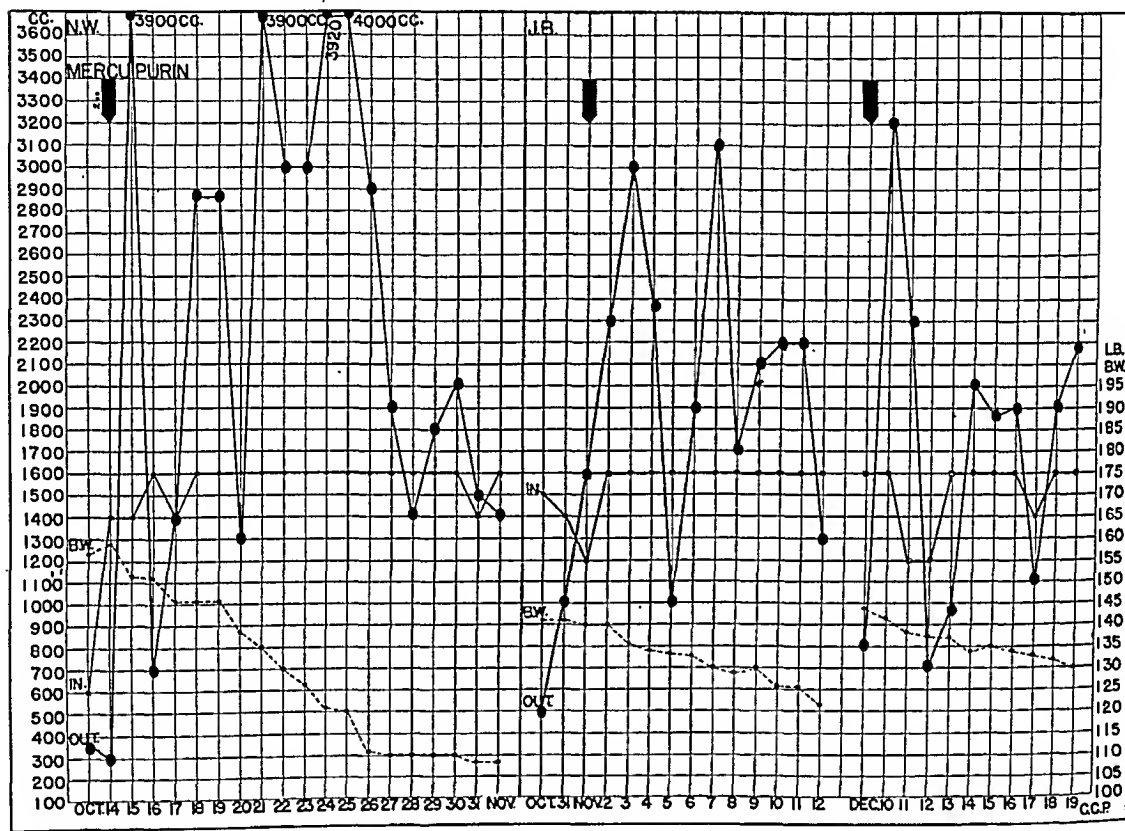


FIG. 5. Fluid output and intake and body weight levels in two edematous patients (N. W. and J. B.), who were given mercupurin intravenously.

The new preparation is said to differ from salyrgan only in that camphoric acid is substituted for salicylic acid. This substitution is said to have made the preparation about half as toxic as well as more effective. The mercurated camphoric acid without the alkaline theophylline added made up in cocoa butter has been distributed as a mercurial diuretic suppository "Mercurin" for rectal administration.

In the clinical studies of DeGraff and his co-workers¹⁶ in 20 edematous patients under carefully controlled conditions with particular respect to the body weight changes, the combination preparation, mercupurin, was given intravenously and was found to produce distinctly better diuresis than the

intravenous injections of the mercurated camphoric acid without the theophylline added. These investigators, therefore, concluded that theophylline contributed definitely to the effectiveness of the mercurial preparations and to the superiority of the new mercurials with theophylline added. They, furthermore, commented on the absence of local reactions and of general toxic mercurial reactions from the intravenous administration of nearly 100 injections. Steurer and Wolpaw¹⁷ reported a very small series of 35 injections and came to conclusions which corroborated those previously made.

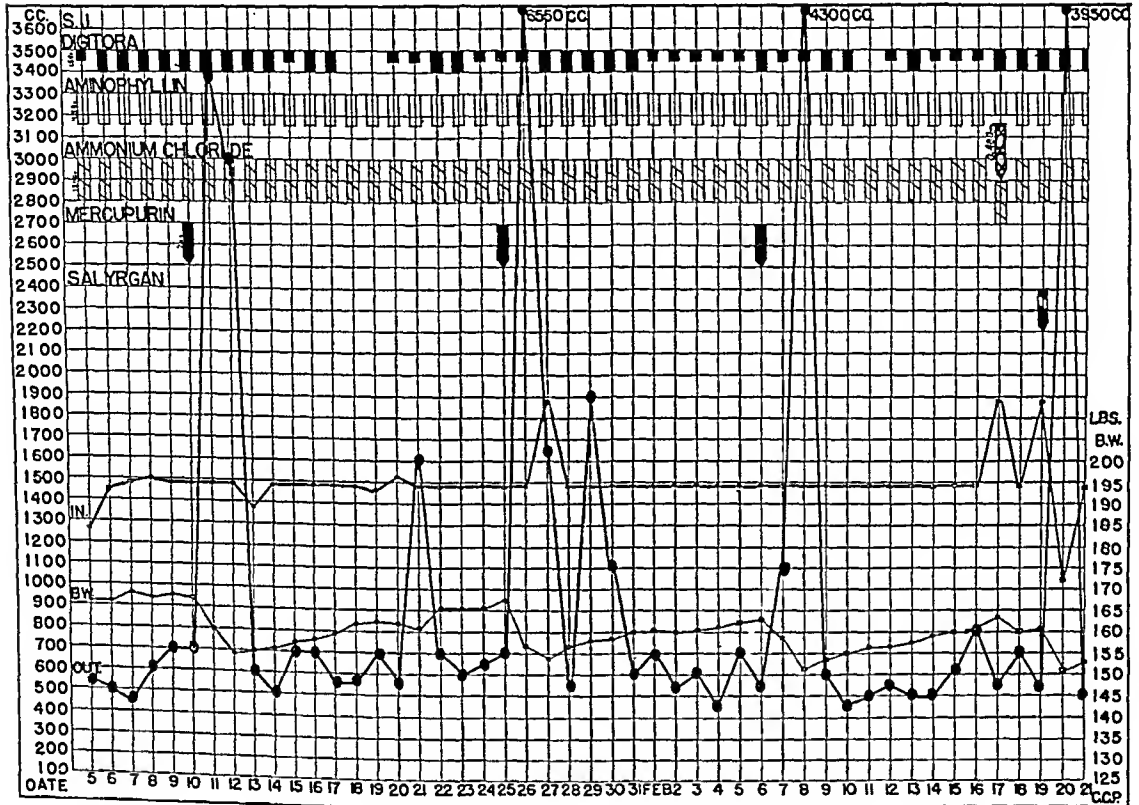


FIG. 6. Fluid output and intake and body weight levels in S. J. in chronic congestive failure treated with constant digitalization, acid salt therapy and aminophylline and fortnightly intravenous injections of mercupurin and lastly aminophylline IV followed by salyrgan.

In England, Parkinson and Thomson¹⁸ have conducted clinical studies of the comparative values of mercupurin and salyrgan intravenously and mercurin administered in suppositories with and without the use of an acid salt. They found that the newer preparations are rather more efficient. Fulton and associates¹⁹ recently reported that the diureses following mercurin suppositories were quite comparable with those obtained by parenterally administered mercurial salts.

OUR CLINICAL STUDIES

Comparative clinical studies of the efficacy of the intravenous administration of mercurials and combinations of diuretics, salyrgan and aminophylline, mercupurin as well as theophylline and digitalis preparations for the same purpose, have been carried out in the wards of the John Sealy Hospital for the past four years. During the second year of our study mercurin suppositories and more recently salyrgan-theophylline injections of 2 c.c. aqueous solution containing 10 per cent salyrgan and 5 per cent theophylline have been under clinical investigation. Our data concern the results of some 600, three day studies on 188 patients with edema, all of whom have been under observation under standard conditions during a preliminary five day rest in bed on a constant intake of 1,400 c.c. of fluid and a standard low protein, salt poor diet.

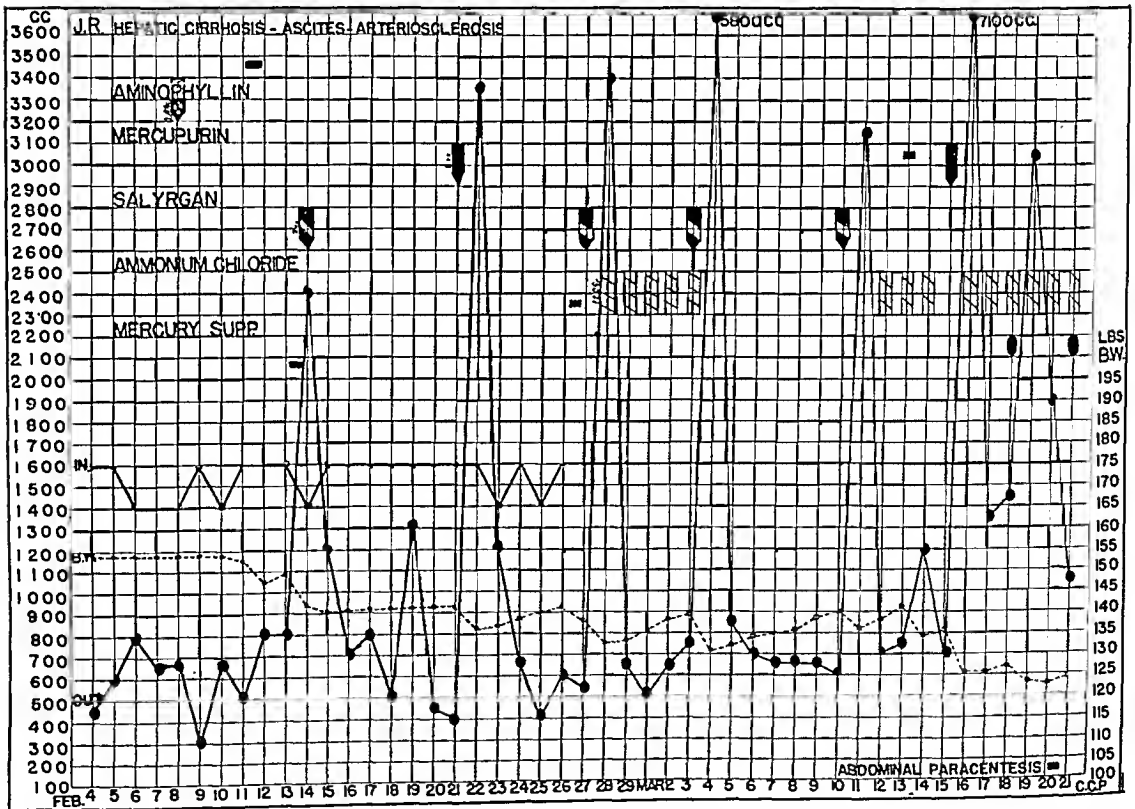


FIG. 7. Diuresis chart of a patient (J. R.) with hepatic (?) cardiac cirrhosis and congestive failure treated with various diuretics and finally with mercurin suppositories.

Only seven of these patients suffered primarily from the effects of cirrhosis of the liver (three of these had syphilitic cirrhosis), two had definitely advanced cardiac cirrhosis. The great majority of cases presented evidences of organic heart disease of one type or another for the most part hypertensive heart disease or syphilitic aortitis with congestive failure in various stages and of varying degree. In these, 366 injections of mer-

cupurin in doses of 2 c.c. of a 13.5 per cent solution were given intravenously alternately with 125 injections of salyrgan given in 2 c.c. doses of 10 per cent solution. A few injections of 2 c.c. of 10 per cent salyrgan and 5 per cent theophylline were recently given and good results recorded. The diuretic results in a series of 100 mercurin suppository administrations were studied. Salyrgan suppositories were not tried in sufficient number for complete study but seem to be more irritating than mercurin. The order of the drug administration was varied so that the same drug was not always used first after the preparatory rest period. Sometimes the preliminary administration and the simultaneous administration of acid salts were carried out; other times these were omitted; while in 25 of the 100 mercurin suppository tests a preparatory enema was omitted.

TABLE I
Summary of Clinical Diuretic Effects

Number of Injections	Drug	Average Increase in Output of Urine			
		1st Day	2nd Day	3rd Day	Total in 3 Days
406	Mercupurin *	503%	180%	95%	778%
125	Mersalyl	341%	120%	62%	523%
29	Salyrgan and Theophylline	458.1%	193.4%	80.12%	732+%
70	Mercurin * Suppositories With Enema	264%	66%	25%	355%
25	Mercurin * Suppositories Without Enema	92%	41%	95%	228%

Recent data compiled by R. Swearingen.

* Supplied by Campbell Products, Inc., 79 Madison Avenue, New York, N. Y.

The summarized results in our diuretic studies are tabulated and the percentage of increases in the urinary output during the first, second and third 24 hour periods following the administration were computed. The output for the preceding or control day was used as the baseline for comparison. The control output of the control day was established in fairly fixed amounts by the conditions of the experiment, namely, the five day rest period preceding the administration. Calculations were done for me by Dr. C. C. Pearson, Dr. R. C. Douglass, Scott Martin, and Revace Swearingen, senior medical students employed under the N. Y. A. fund.

CLINICAL SUMMARY OF DIURETIC EFFECTS

A survey of all the data, taking into account the fact that the conditions were varied, now in favor of one drug and now in favor of the other, seems to show an advantage in favor of the combination preparation. Mercupurin seems to be the most efficient diuretic and at the same time the safest in as much as we have had no evidences of unfavorable reaction in over 400 intravenous injections. The new salyrgan-theophylline promises to be

a similarly most effective anti-edemic preparation. Mercury suppositories produced a diuresis in almost half of the cases during the first 24 hours after treatment; occasionally there was an increase for the three days following their use. A definitely better effect was obtained when an enema was used to prepare the bowel. Preliminary or concomitant administration of an acid salt likewise distinctly augmented the diuresis which resulted from mercurin suppositories as well as that from intravenous mercurials or combinations. Our results with the suppositories, however, have not been as spectacular as those reported by other investigators. In one instance we have noted renal irritation following the use of the newer preparation and in this case it appeared in a patient who had been previously given the intravenous mercurial without complications. Proctitis of a rather severe type was occasionally noted.

COMMENTS

The results of the studies of the combination of mercurials and xanthines bear out the prediction of our earlier studies in which we pointed out the

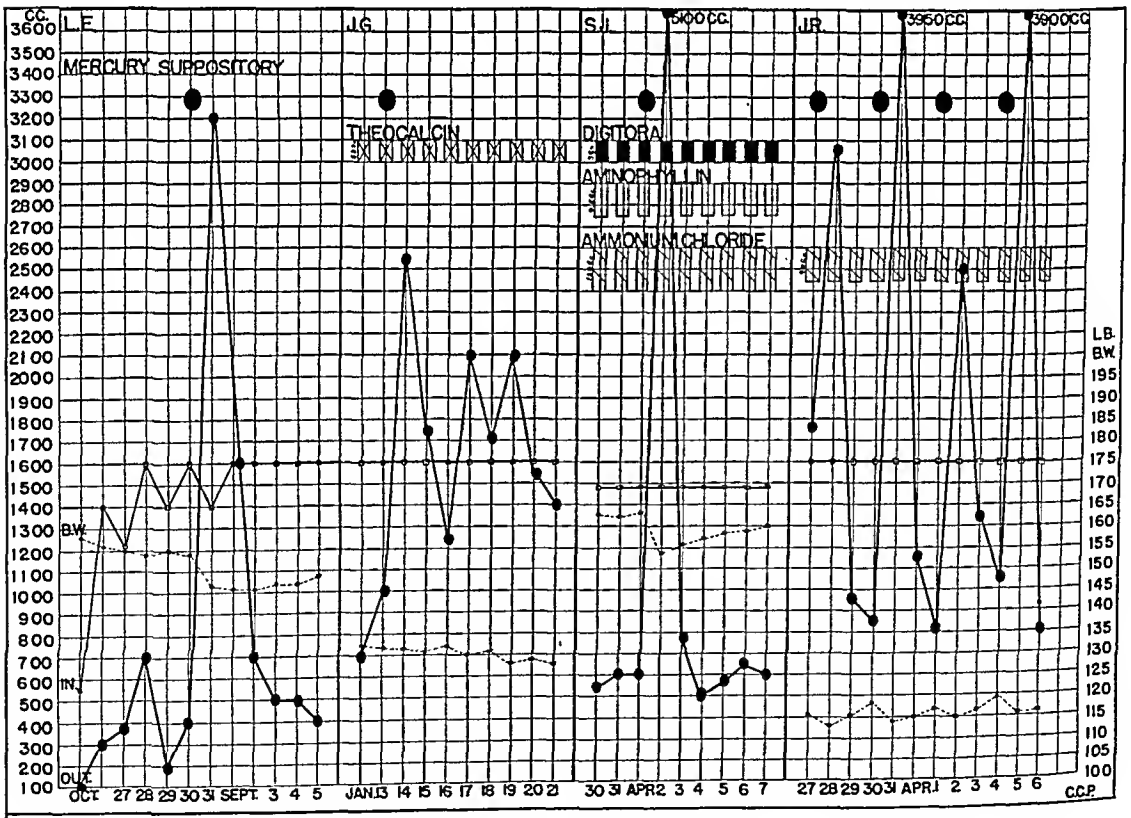


FIG. 8. Partial diuresis charts of four patients in whom mercurin suppositories were used.

augmentary effect of theophylline in combination with mercurials. Our clinical findings further confirm these contentions and those of some investigators in that the combination preparations of xanthines and mercurials

have advantages in the matter of diuretic efficiency as well as in safety over the pure mercurials.

The development of a mercurin suppository is a worthwhile forward step, even though they are effective in perhaps only 40 per cent of the cases and occasionally cause an albuminuria. It will be remembered that theophylline may be given by mouth in such instances and a combination effect may be secured. The acidosis producing salts, ammonium chloride or nitrate, are as a rule well tolerated but in nephritics with nitrogen retention they should not be used. Ammonium nitrate is better tolerated and hence preferable in cases in which renal function is borderline.

REFERENCES

1. HERRMANN, GEORGE and DECHERD, G. M., JR.: The chemical nature of heart failure, *ANN. INT. MED.*, 1939, xii, 1233.
 - (a) HERRMANN, GEORGE: Serum calcium, inorganic phosphorus and plasma proteins in cardiac edema and after diuresis, *Proc. Soc. Exper. Biol. and Med.*, 1930, xxviii, 263.
 - (b) Some observations of the relation of blood chemical findings to cardiac function. Plasma proteins in congestive heart failure, *Trans. Assoc. Am. Phys.*, 1931, lvi, 360.
 - (c) Some blood chemical findings in congestive failure before and after treatment, *South. Med. Jr.*, 1932, xxv, 934.
 - (d) A possible biochemical basis of heart failure, *Med. Papers dedicated to Dr. Henry A. Christian*, 1936, i, 17.
 - (e) —, with DECHERD, G., and SCHWAB, E. H.: Some biochemical factors in heart failure, *South. Med. Jr.*, 1936, xxix, 386.
 - (f) —, and DECHERD, G.: Insufficiencia Cardiaca en Terminos Bioquimicos, *Arch. Latinos Amer. de Cardiol. y. Hematol.*, 1936, vi, 49.
 - (g) —, and DECHERD, G.: Creatine mobilization in myocardial damage, *Proc. Soc. Exper. Biol. and Med.*, 1934, xxxii, 477.
 - (h) —, DECHERD, G., and ERHART, P.: Total creatine content of perfused rabbit hearts, *Proc. Soc. Exper. Biol. and Med.*, 1934, xxxii, 547.
 - (i) DECHERD, G., and DAVIS, O.: Further rabbit heart perfusion experiments with amino-acids, *Proc. Soc. Exper. Biol. and Med.*, 1935, xxxii, 1302.
 - (j) —, and DECHERD, G.: Creatine and glycogen content of normal and infarcted heart muscle of the dog, *Proc. Soc. Exper. Biol. and Med.*, 1935, xxxii, 1304.
 - (k) —, and DECHERD, G.: Creatine metabolism with especial reference to heart disease, *Jr. Lab. and Clin. Med.*, 1935, xx, 890.
 - (l) —, and DECHERD, G.: The effect of myocardial destructive agents on the creatine and glycogen content of the rabbit heart, *Proc. Soc. Exper. Biol. and Med.*, 1936, xxxiii, 519.
 - (m) DECHERD, G., SCHWAB, E. H., and BROWN, W. O.: The creatine content of the hypertrophied rabbit heart muscle, *Proc. Soc. Exper. Biol. and Med.*, 1936, xxxiii, 522.
 - (n) —, and DECHERD, G., SCHWAB, E. H., and ERHART, P.: The creatine content of the digitalized normal and hypertrophied rabbit heart muscle, *Proc. Soc. Exper. Biol. and Med.*, 1936, xxxiii, 521.
2. HARRISON, T. R.: Failure of the circulation, 1935, Williams and Wilkins Co., Baltimore.
3. CLOETTA, MAX: Ueber den Einfluss der chronischen Digitalisbehandlung auf das normale and pathologische Herz, *Arch. f. exper. Pathol. u. Pharmakol.*, 1908, lix, 209.
4. CHRISTIAN, H. A.: The use of digitalis other than in the treatment of cardiac decompensation, *Jr. Am. Med. Assoc.*, 1933, c, 789.
5. FRIEDMAN, B., RESNIK, H., JR., CALHOUN, J. A., and HARRISON, T. R.: Effect of diuretics on the cardiac output of patients with congestive heart failure, *Arch. Int. Med.*, 1935, lvi, 341.

6. GOLD, H., KWIT, N. T., and OTTO, H.: Xanthines (theobromine and aminophyllin) in treatment of cardiac pain, *Jr. Am. Med. Assoc.*, 1937, cviii, 2173.
7. PAULLIN, J. E., and MINNICH, W. R.: The treatment of congestive heart failure, *South. Med. Jr.*, 1936, xxix, 400.
8. HOUSTON, W. R.: Personal communication, and "The Art of Treatment," 1936, Macmillan Co., N. Y.
9. BARKER, M. H.: Edema as influenced by low ratio of sodium to potassium intake. Clinical observations, *Jr. Am. Med. Assoc.*, 1932, xcvi, 2193-2197.
10. KEITH, N. M., BARRIER, C. E., and WHELAN, M.: The diuretic action of ammonium chloride and novasurol, *Jr. Am. Med. Assoc.*, 1925, lxxxv, 799.
11. CHRISTIAN, H. A.: Oedema, diuretics, diuresis (Frank Billings Lecture), *Proc. Inst. Med. Chicago*, 1936, xi, 149.
 - (a) TAINTER, M. L., and DOCK, WM.: Further observations on circulatory actions of digitalis and strophanthus with special reference to liver and comparisons with histamine and epinephrine, *Jr. Clin. Invest.*, 1930, viii, 485-503.
12. STOLL, ARTHUR: The cardiac glucosides, 1936, The Pharmaceutical Press, London, W. C. 1.
 - (a) LEWIS, SIR THOMAS: Diseases of the heart, 1933, Macmillan Co., New York.
 - (b) WAYNE, E. J.: *Clin. Sci.*, 1933, i, 63.
 - (c) STROUD, W. D.: Personal communication.
13. HERRMANN, G., STONE, C. T., and SCHWAB, E. H.: Some studies in the mechanism of diuresis in patients with congestive heart failure, *Trans. Assoc. Am. Phys.*, 1932, lvii, 279.
 - (b) HERRMANN, G., STONE, C. T., SCHWAB, E. H., and BONDURANT, W. W.: Diuresis in patients with congestive heart failure, *Jr. Am. Med. Assoc.*, 1932, xcix, 1647.
 - (c) HERRMANN, G., SCHWAB, E. H., and STONE, C. T.: Further studies on the mechanism of diuresis in patients with congestive heart failure, *Trans. Assoc. Am. Phys.*, 1933, lviii, 364.
 - (d) HERRMANN, G., SCHWAB, E. H., STONE, C. T., and MARR, W. L.: On the advantage of alternating the vegetable and metallic diuretics in the treatment of edema of congestive heart failure, *Jr. Lab. and Clin. Med.*, 1933, xviii, 902.
 - (e) SCHWAB, E. H., HERRMANN, G., and STONE, C. T.: The complementary action of certain antiedemic drugs, *Texas State Jr. Med.*, 1933, xxix, 240.
 - (f) STONE, C. T., HERRMANN, G., and SCHWAB, E. H.: The treatment of edema in congestive heart failure, *South. Med. Jr.*, 1934, xxvii, 113.
 - (g) HERRMANN, G. R.: Mercurial diuretics. *Cyclopedia of medicine*, 1936, Davis, Philadelphia, xiii, 45.
14. SCHMITZ, H. L., and LEITER, L.: A comparative study of the diuretic action of euphyllin and salyrgan, *Jr. Clin. Invest.*, 1931, x, 667.
15. v. ISSEKUTZ, B., and v. VEGH, F.: Über die diuretische Wirkung organischer Quecksilberverbindungen, *Arch. f. exper. Path. u. Pharmacol.*, 1928, cxxxviii, 245.
16. DEGRAFF, A. C., NADLER, J. E., and BATTERMAN, R. C.: A study of the diuretic effect of mercupurin in man, *Am. Jr. Med. Sci.*, 1936, cxc, 526.
17. STEUER, L. G., and WOLPAW, S. E.: The diuretic action of mercupurin, *Jr. Lab. and Clin. Med.*, 1935-36, xxi, 298.
18. PARKINSON, J., and THOMSON, W. A. R.: A mercurial (novurit) suppository as a diuretic for cardiac oedema, *Lancet*, 1936, i, 16.
19. FULTON, M. N., and BRYAN, A. H.: Some observations on the comparative effectiveness of mercurial diuretics with and without theophylline (mercupurin, salyrgan, etc.), *Jr. Lab. and Clin. Med.*, 1934-35, xx, 1252.
20. HERRMANN, G., and DECHERD, G. M., JR.: Further studies on the mechanism of diuresis with especial reference to the action of some newer diuretics, *Jr. Lab. and Clin. Med.*, 1937, xxii, 767.

INTERPRETATION OF THE ELECTROCARDIOGRAPHIC FINDINGS IN CALCAREOUS STENOSIS OF THE AORTIC VALVE*

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IN the last few years distinct progress has been made in the clinical recognition of calcareous stenosis of the aortic valve. This is clearly exemplified by the fact that, as late as 1931, the lesion was only occasionally identified during the life of the patient whereas, today, its recognition is virtually a routine procedure. This high degree of diagnostic proficiency is chiefly the result of a determined and sustained effort to correlate the clinical signs with the postmortem findings. This has made the clinician alert, guiding him to utilize a special fluoroscopic technic^{4, 6, 8, 9, 10} which in a remarkably high percentage of cases permits the demonstration of calcium in the valve leaflets, annulus, or both.

A clearer understanding of this lesion^{2, 3, 5} has stimulated renewed interest in its various manifestations and necessitates a revision of current impressions regarding its incidence and the forms which it may assume. In a recent publication by Clawson and his coworkers, dealing exclusively with representative postmortem material, they were able to demonstrate calcium by gross methods of examination in 84 per cent of all cases of nonsyphilitic deformities of the aortic valve. In our recent survey of postmortem material at The Mayo Clinic⁵ we found no instance of aortic stenosis without some deposit of calcium. Further to illustrate the fact that calcareous aortic stenosis is not a rare finding we cite this recent study⁵ which revealed that this lesion occurs in 18.1 per cent of all cases of healed valvular defects encountered in routine postmortem examinations.

It therefore seems appropriate to call attention to additional diagnostic methods as they apply to the identification of this interesting valvular deformity. We refer to the occurrence and interpretation of electrocardiographic abnormalities.

MATERIAL

This study is based on 176 cases of calcareous aortic stenosis in which the electrocardiographic records were available. In 63 cases (35.8 per cent) the diagnosis was confirmed at necropsy and in 113 cases (64.2 per cent), the identification of the lesion was determined by clinical means together with fluoroscopic demonstration of calcification of the aortic leaflets or annulus.

In the postmortem material the degree of stenosis was distributed in the following manner: it was of grade 4 in 12 cases, of grade 3 in 28, of

* Received for publication April 23, 1938.

grade 2 in 20, and of grade 1 in three. It was shown in our previous study⁵ that the degree of calcification closely paralleled the degree of stenosis. In 85 of the cases in which postmortem examination was not conducted, the diagnosis of calcareous aortic stenosis was made on the basis of the presence of classical physical signs and the clear-cut demonstration of calcification of the aortic valve by fluoroscopic means. In the remaining 28 cases in this group we concluded that the degree of stenosis was slight owing to the fact that all the classical physical signs were not present although calcification was demonstrable by fluoroscopy. These cases presented findings comparable with those of stenosis of grade 1 occurring in our postmortem material.

FACTORS INFLUENCING THE ELECTROCARDIOGRAM

The effect of a stenotic aortic orifice on the heart is obvious. The tremendous load imposed on the left ventricle becomes evident when one visualizes the extremely small opening that so frequently offers the only route for blood to gain entrance to the aorta. Increased work obviously eventuates in hypertrophy, and the most marked examples of cardiac hypertrophy are found in cases of marked calcareous stenosis of the aortic valve. In two cases in our series the heart weighed more than 1000 gm.

In cases in which aortic stenosis occurs as a solitary lesion, there being no additional factors to impose a further load on the heart, the stress is principally borne by the left ventricle. When aortic insufficiency occurs, hypertrophy of all the cardiac chambers may ensue, as shown by the studies of Levine and Carr. In our material the stenotic lesion was complicated by aortic insufficiency in 34.6 per cent of the cases. When mitral stenosis and other lesions exerting strain on the right ventricle coexist, this chamber hypertrophies and both sides of the heart participate in varying degrees in sharing the abnormal strain.

These facts are emphasized because a knowledge of physiologic principles is necessary to an interpretation of the electrocardiographic findings. On critical analysis of the electrocardiograms and careful correlation of the data obtained with the postmortem findings, it became evident that the established physical laws of electrocardiographic behavior¹ prevailed in this study. In the case of a lesion that predominantly imposes strain on the left ventricle it may be anticipated that the prevailing electrocardiographic configuration will reflect this strain, as evidenced by records displaying left axis deviation and T-wave negativity in Lead I or in Leads I and II. Exceptions to this are usually explained by antagonistic strain, myocardial injury, such as acute or healed infarcts, and the effect of digitalis, especially when administered in large quantities over a considerable period of time.

ANALYSIS OF POSTMORTEM MATERIAL

Postmortem examination was conducted in 63 of the 176 cases of calcareous aortic stenosis (35.8 per cent) and these cases will be considered first and the data derived will then be applied to the clinical cases (table 1).

No Evidence of Ventricular Strain. Only six of the 63 cases (9.5 per cent) showed no electrocardiographic evidence of preponderant ventricular strain. In three cases, however, antagonistic right ventricular strain was coexistent, and this apparently neutralized the effect of the stenotic aortic

TABLE I
Evidence of Predominant Ventricular Strain *
Electrocardiographic Summary

Material	Cases	Per cent	No Ventricular Strain	Left Ventricular Strain	Right Ventricular Strain	T-wave Negativity in Leads I, II and III
Postmortem cases †	63	35.8	6	37	10	10
Clinical cases (marked stenosis)	85	48.3	12	50	7	16
Clinical cases (slight stenosis)	28	15.9	6	18	3	1
Total number	176		24	105	20	27
Per cent		100	13.6	59.7	11.4	15.3

* Associated valvular deformities and other lesions occurring in these groups are detailed in the text.

† All degrees of stenosis occur in this group.

orifice. There were three cases of well-marked mitral stenosis and in one case there was an associated mitral stenosis and aortic insufficiency. Auricular fibrillation was present in two cases.

Evidence of Left Ventricular Strain. Electrocardiographic evidence of left ventricular strain included left axis deviation and T-wave negativity (also diphasic T-waves) in Lead I or Leads I and II. Thirty-seven cases (58.7 per cent) presented these findings. In 20 cases T-wave negativity occurred in electrocardiograms with left axis deviation, in 14 cases left axis deviation was unassociated with T-wave negativity, and in three cases T-wave negativity occurred without axis deviation.

In seven cases mitral stenosis was also present; it was of grade 2 in five cases and of grade 3 in two cases. In eight cases there was an associated aortic insufficiency, in one of them in conjunction with mitral stenosis. In one case presenting left axis deviation, T-wave negativity in Leads I and II and auricular fibrillation, the calcareous deposit at the aortic valve extended into the aorta, almost completely obliterating the ostium of the left coronary artery and also reducing the size of the ostium of the right coronary artery.

When cases displaying evidence of left ventricular strain were analyzed according to the degrees of aortic stenosis, it was found that in two-thirds of them (64.8 per cent) the stenotic process was marked (grade 4 and 3), whereas in the remaining third (35.2 per cent), lesser degrees of stenosis were present (grades 2 and 1).

The weight of the heart ranged from 265 to 1170 gm., the average weight being 593.6 gm. Some interesting facts were gleaned on further analysis of these data, illustrating the fact that the presence of T-wave negativity in the electrocardiogram is proof of greater ventricular strain than axis deviation alone. When left axis deviation was the only graphic evidence of left ventricular strain the weight of the heart ranged from 265 to 875 gm., the average weight being 505.1 gm.; when in addition T-wave negativity in Lead I or in Leads I and II was present, the weight of the heart was considerably greater. The lowest weight was 356 gm. and the highest was 1170 gm.; the average weight was 650.5 gm., or an average of 145.4 gm. greater than in cases displaying only left axis deviation.

There were only five cases (13.5 per cent) of auricular fibrillation in this group and in no instance was mitral stenosis an associated finding.

Evidence of Right Ventricular Strain. In this group of cases the electrocardiograms exhibited either right or left axis deviation and T-wave negativity (also diphaseic T-waves) in Leads II and III. There were 10 such cases (15.9 per cent); all but two showed T-wave negativity and these displayed right axis deviation and auricular fibrillation. Six cases showed right axis deviation, three left axis deviation, and the remaining one showed no axis deviation but T-wave negativity in Leads II and III.

Cases presenting evidence of predominant right ventricular strain in the presence of a mechanical barrier that outstandingly imposes its burden on the left ventricle are obviously of unusual interest as at first glance they appear to be exceptions to the recognized laws of electrocardiography. When these cases received critical analysis and when the additional findings were carefully appraised, however, it was found that only two remained exceptions to the general rule. Five cases showed well-marked mitral stenosis (grades 3, 3, 3, 2, 2); in three of them there was an associated aortic insufficiency and, in one case, digitalis had been administered beyond the point of tolerance. The sixth patient presented an advanced degree of pulmonary arteriolar atherosclerosis, a disease notorious for its imposition of work on the right ventricle. The seventh and eighth patients both had infarction of the posterior basal portion of the left ventricle which characteristically results in T-wave negativity in Leads II and III. The infarcts in both cases were old but their presence remained as electrocardiographic relics.

In analyzing these cases in which the electrocardiograms displayed predominant strain of the right ventricle with reference to the degree of aortic stenosis it was found that, in five, the stenotic process was marked (grades 4 and 3), in five there were lesser degrees of stenosis (grade 2). However, in two cases in which the degree of aortic stenosis was marked, healed infarcts involved the posterior basal surface of the left ventricle.

The weight of the heart in this group ranged from 360 to 862 gm., the average weight being 629.3 gm., or a value slightly greater than the average weight of the heart for cases showing evidence of predominant strain of the left ventricle (593.6 gm.).

Auricular fibrillation occurred in three cases (30 per cent), which was a relatively higher incidence than in cases showing predominant left ventricular strain (13.5 per cent). In two cases mitral stenosis and aortic insufficiency were associated findings.

Cases Presenting T-wave Negativity in Leads I, II, and III. These cases are of unusual interest and combine certain features of the two preceding groups. There were 10 cases (15.9 per cent) in this group. There were no instances of right axis deviation; four cases showed left axis deviation, and in the remaining six cases no axis deviation occurred. Only one case with mitral stenosis was recorded (grade 3). Aortic insufficiency was present in half the cases, and in one of them the pericardial cavity was almost obliterated by old adhesions. In another case the deposit of calcium at the aortic valve extended downward to invade the aortic cusp of the mitral valve and upward into the aorta, partially occluding the ostium of the left coronary artery. Thus there were only three cases in this group in which no lesions except the aortic stenosis were demonstrable. Marked degrees of aortic stenosis (grades 4 and 3) were present in all cases except one (grade 2).

The weight of the heart ranged from 434 to 892 gm., the average weight being 581.6 gm. This average weight was quite comparable to that for cases showing evidence of predominant left ventricular strain (593.6 gm.).

Auricular fibrillation occurred in only one case.

Disturbances in Cardiac Conduction. Defects in cardiac conduction were recorded in only eight cases (12.7 per cent). There was one case with complete heart block in which the nodular excrescence of calcium extended from the mitral cusp of the aortic valve in such a manner as to involve the bundle of His. There were four instances of incomplete bundle-branch block and three cases showed evidence of delayed auriculoventricular conduction.

Comment. Only eight of the 63 cases in this group proved on analysis to be exceptions to the general laws of electrocardiographic behavior. In three cases there was no evidence of predominant ventricular strain, in two cases there was predominant right ventricular strain, and in three cases there was T-wave negativity in Leads I, II and III. In spite of these exceptions, however, the correlations for the group were remarkably accurate.

ANALYSIS OF CLINICAL CASES SHOWING MARKED CALCAREOUS STENOSIS

There were 85 cases (48.3 per cent of the total of 176) in which the clinical findings unequivocally demanded the diagnosis of calcareous stenosis of the aortic valve and in which fluoroscopic examination clearly demonstrated calcification of the aortic leaflets or annulus. When the clinical findings in this group were compared to those in the postmortem group they were found to agree closely in respect to the more marked grades of stenosis,

permitting the presumption that this group of clinical cases represented well-advanced examples of calcareous aortic stenosis.

No Evidence of Ventricular Strain. In 12 (14.1 per cent) of the cases there was no graphic evidence of preponderant ventricular strain, that is, axis deviation and T-wave negativity. There were no instances of mitral stenosis, but aortic insufficiency was present in seven cases. Auricular fibrillation was recorded in one case.

Evidence of Left Ventricular Strain. It is interesting to note how closely the data for this group of cases agree with those for the postmortem group. Fifty cases (58.8 per cent) revealed electrocardiographic evidence of predominant strain on the left ventricle. In 25 cases T-wave negativity in Lead I or in Leads I and II occurred in electrocardiograms showing left axis deviation; in 19 cases left axis deviation was unassociated with T-wave negativity and in six cases T-wave negativity occurred without left axis deviation.

Mitral stenosis was identified in only two cases. The recognition of mitral stenosis in the presence of well-marked stenosis of the aortic valve is often difficult owing to the fact that the extremely loud and rough systolic murmur of the aortic lesion with its widespread propagation may obliterate the less conspicuous signs of mitral stenosis. This undoubtedly accounts for the extremely low incidence of mitral stenosis in this group. Aortic insufficiency occurred in 21 cases. Auricular fibrillation was recorded in nine cases (18 per cent), and was associated with aortic insufficiency in five cases.

Evidence of Right Ventricular Strain. Seven cases (8.2 per cent) comprised this group. In two cases the electrocardiograms revealed right axis deviation in addition to T-wave negativity in Leads II and III. It is significant to note that mitral stenosis was diagnosed in six cases. The fact that mitral stenosis was identified in such a high percentage of cases in this group suggests the probability that the lesion was well marked and therefore its clinical expressions were not obscured by those of the stenotic aortic valve. It is also possible that the degree of mitral stenosis exceeded that of the aortic valve. Four cases also showed aortic insufficiency, in each case coexistent with mitral stenosis.

Auricular fibrillation occurred in three cases (42.9 per cent) of this group, in each instance in cases with mitral stenosis and aortic insufficiency.

Cases Presenting T-Wave Negativity in Leads I, II and III. There were 16 cases (18.9 per cent) showing this electrocardiographic configuration. Left axis deviation occurred in four cases, right axis deviation in two, and there was no axis deviation in 10 cases. Mitral stenosis was identified in only one case, while aortic insufficiency occurred in eight cases. One patient had received digitalis beyond the limit of tolerance and this may have influenced the electrocardiogram.

No instance of auricular fibrillation was recorded in this group.

Disturbances in Cardiac Conduction. In two cases there was complete heart block, in six incomplete bundle-branch block, and in one case there was complete left bundle-branch block. In five other cases delayed auriculo-ventricular conduction was demonstrated.

ANALYSIS OF CLINICAL CASES SHOWING ONLY SLIGHT CALCAREOUS STENOSIS

In this group of 28 cases all the clinical signs of calcareous stenosis of the aortic valve were not present but fluoroscopic examination revealed the presence of calcium in the valve leaflets or annulus. The clinical findings in this group closely corresponded with those for grade 1 stenosis in the post-mortem material and are assumed to represent similar cases.

No Evidence of Ventricular Strain. There were six cases (21.4 per cent) without axis deviation or T-wave negativity. No associated valvular lesions were demonstrated and there was no instance of auricular fibrillation.

Evidence of Left Ventricular Strain. There were 18 cases (64.3 per cent) presenting electrocardiographic evidences of predominant strain on the left ventricle. In five cases T-wave negativity in Lead I or Leads I and II occurred in records showing left axis deviation, in 11 cases left axis deviation occurred without T-wave negativity and in two cases, T-wave negativity occurred without axis deviation.

There was no instance of mitral stenosis in this group but, in three cases, aortic insufficiency occurred. Auricular fibrillation was present in only one case.

Evidence of Right Ventricular Strain. These findings occurred in three cases (10.7 per cent). T-wave negativity in Leads II and III was recorded in two cases, one of which showed left axis deviation. In the third case the electrocardiogram showed right axis deviation. There was no instance of mitral stenosis, but there was one case with aortic insufficiency. Auricular fibrillation was not observed.

Cases Presenting T-wave Negativity in Leads I, II and III. There was only one case (3.6 per cent) in this group. No associated valvular defects were noted.

Disturbances in Cardio-Conduction. None were observed in the cases in this group.

SUMMARY

The electrocardiographic findings in 176 cases of calcareous stenosis of the aortic valve are presented. The records were analyzed with special reference to graphic configurations conforming to the generally accepted laws of predominant ventricular strain. A very high correlation between electrocardiographic variations and pathologic lesions was disclosed for the postmortem material, only eight cases proving to be exceptions to the rule.

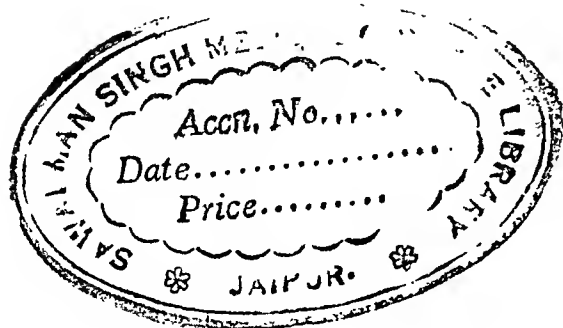
In clinical cases the same opportunity for comparable correlations was

obviously not afforded, although a similar tendency toward correlation was disclosed when the data on the postmortem cases were applied to them.

Auricular fibrillation occurred infrequently, only 25 instances (14.2 per cent) being recorded for the entire series. In six cases auricular fibrillation occurred in the presence of mitral stenosis and aortic insufficiency, and in seven other cases in the presence of aortic insufficiency alone.

REFERENCES

1. BARNES, A. R., and WHITTEN, M. B.: Study of T-wave negativity in predominant ventricular strain, *Am. Heart Jr.*, 1929, v, 14-67.
2. CHRISTIAN, H. A.: Aortic stenosis with calcification of the cusps; a distinct clinical entity, *Jr. Am. Med. Assoc.*, 1931, xcvi, 158-161.
3. CLAWSON, B. J., NOBLE, J. F., and LUFKIN, N. H.: The calcified nodular deformity of the aortic valve, *Am. Heart Jr.*, 1938, xv, 58-76.
4. CUTLER, E. C., and SOSMAN, M. C.: Calcification in the heart and pericardium, *Am. Jr. Roentgenol.*, 1924, xii, 312-320.
5. DRY, T. J., and WILLIUS, F. A.: Calcareous disease of the aortic valve: a study of 228 cases, *Am. Heart Jr.*, 1939, xvii, 138-157.
6. FLEISCHNER, F.: Verkalkung des Annulus fibrosus, *Wien. med. Wchnschr.*, 1925, lxxv, 2721.
7. LEVINE, VICTOR, and CARR, J. G.: Cardiac weights, *Arch. Int. Med.*, 1933, lxi, 429-446.
8. PARADE, G. W., and KUHLMANN, F.: Verkalkungen des Herzskeletts im Röntgenbild, *München. med. Wchnschr.*, 1933, i, 99-100.
9. SOSMAN, M. C., and WOSIKA, P. H.: Calcification in aortic and mitral valves: with a report of 23 cases demonstrated in vivo by the roentgen-ray, *Am. Jr. Roentgenol.*, 1933, xxx, 328-348.
10. WILLIUS, F. A., and CAMP, J. D.: Clinical and roentgenologic comments on calcareous aortic stenosis, *Med. Clin. N. Am.*, 1935, xix, 487-497.



ASTHMATOID HEART FAILURE; A FORM OF LEFT VENTRICULAR FAILURE AND ITS DIFFERENTIATION FROM BRONCHIAL ASTHMA BY CIRCULATION TIME AND OTHER CRITERIA *

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THE diagnosis of bronchial asthma on an allergic basis when symptoms appear for the first time late in life should be made with great caution. Only 12 to 18 per cent of all cases have their onset in the fifth and sixth decades and less than 2 per cent after the age of sixty.¹ It is during this period of life that many of the conditions which must be considered in the differential diagnosis of bronchial asthma first make their appearance and all of these should be ruled out before the presumptive diagnosis of allergic asthma can be made.

Prominent among the diseases presenting difficulties in diagnosis is heart failure. It is the purpose of this paper to reemphasize this important point in differential diagnosis, to reiterate the criteria of differentiation and to point out that some forms of left ventricular failure produce a paroxysmal dyspnea indistinguishable by symptoms, physical signs or therapeutic response from bronchial asthma.

In an excellent clinical and pathological consideration of fatal "asthma," Lamson and Butt² have shown how often patients with true allergic asthma have and succumb to cardiac disease and how often the wheezing of patients diagnosed as having asthma is shown at autopsy to be the result of renal, cardiac, bronchial or neoplastic disease. They cite insurance statistics³ to show how much higher the death rate is among asthmatics as compared with the expected average. Much of this excess occurs in deaths which are the results of organic heart disease and Dublin and Marks⁴ have shown that in male asthmatics the heart disease mortality is two and one-third times the normal. It is not quite clear from their statistics whether the diagnoses of bronchial asthma were erroneous or whether the incidence of heart disease was greater among allergic asthmatics. Both factors are probably operative, but in any case it should be quite clear that the belief of many clinicians that bronchial asthma carries with it an excellent life expectancy and may be treated as an essentially harmless disease should be revised.

As has been pointed out before, the term bronchial asthma is used in this paper in the restricted sense of allergic asthma but is often used more loosely. Bronchial asthma has been defined as¹⁷ "a form of paroxysmal dyspnea, the characteristic feature of which is a marked diminution or arrest of the respiratory movement with prolonged expiration." If this definition is

* Received for publication October 25, 1937.

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accepted and if cognizance is taken of the origin of the word (from the Greek "hard breathing") then it is justifiable to apply the term asthma to any condition which satisfies the definition of Norris and Landis. Certainly the use of "cardiac asthma" to cover the several forms of paroxysmal dyspnea in heart disease is etymologically correct and convenient.⁵

In this paper the terms cardiac asthma and left ventricular failure will be applied only to those forms of failure in which wheezing respirations are the dominant feature. Other types of left ventricular failure, while clinically important, have been disregarded in this study. Those cases in which there was wheezing respiration without basal or moist râles so that the physical signs resembled closely those of bronchial asthma have been called "asthmatoïd" heart failure.

PATHOGENESIS OF THE PAROXYSM OF CARDIAC ASTHMA

During an attack of cardiac asthma the patient will be found to present two sets of pulmonary signs: the first, those present before the attack, such as basal râles, signs of effusion, pneumonitis, atelectasis, infarction, emphysema, etc., and the second, an accentuation of these signs or, more often, new, temporary signs, conspicuously, wheezing respiration, prolonged expiration, basal râles not previously present and signs of pulmonary edema. Most often the second group is dependent, according to modern concepts of the pathogenesis, on left ventricular weakness and on pressure differences between the right and left sides of the heart leading to sudden damming of blood in the pulmonary circuit. There are some cases, such as those attacks of paroxysmal dyspnea occurring as an initial symptom in cerebral embolism or embolism elsewhere, which may be dependent on reflex nervous influences acting through or independent of changes in the pulmonary circulation. In any event, disregarding basal or bubbling râles which cannot be confused as a rule with bronchial asthma, the signs are dependent on the same factors as those concerned in allergic asthma; namely, narrowing of the lumina of the smaller bronchioles either by direct muscular spasm or by swelling of the bronchiolar mucosae or by edema fluid or other detritus obstructing the lumen. Temporary emphysema may also play a rôle. These changes usually differ in degree and in quality from those observed in allergic asthma so that, although asthmatoïd breathing is often a conspicuous feature, there is seldom any question of differential diagnosis. Occasionally, as we shall see, asthmatoïd respirations and wheezes may dominate the picture so completely that accurate diagnosis is often impossible during the attack.

Bronchial spasm may actually occur, according to MacKenzie,⁶ as a reflex disturbance produced by the weakened heart. I believe that if reflex bronchial spasm occurs, it may follow changes other than sudden cardiac weakness, such as cerebral embolism. As Pratt points out, peripheral factors must be considered in view of the hypertension, profuse sweating and

cold skin which are often found indicating peripheral vasomotor changes and an associated "medical shock" may be present. Eppinger and others⁷ showed that in some cases the blood flow from the arteries to the veins is increased during cardiac asthma.

Excellent accounts of the pathological changes in the lungs have been published so that here the discussion will be confined to those changes which may produce wheezing respiration.⁸ Microscopically the air space is diminished by an intense engorgement of the capillaries which may protrude far into the alveoli which contain erythrocytes, leukocytes, desquamated alveolar epithelia and large mononuclear cells containing hemosiderin, the heart failure cells. Hyperplasia of the collagenous framework and of the reticulum, elastic and muscle fibers may occur. Corpora amylacea are not uncommon. When pulmonary edema supervenes, the alveoli, bronchioles, bronchi and trachea may be filled by frothy fluid. "Pulmonary edema differs from edema in other parts of the body in that the fluid is not almost entirely in the interstices of the tissue, but much more in the alveolar lumens, which are really outside of the physiological interior of the body. The reason for this peculiarity seems to be in the morphological adaptation of the lung to its respiratory function. The capillaries lie very close to the surface of the alveoli and are covered by only a thin layer of alveolar epithelium, which probably does not form a continuous covering. The result is that fluid which transudes from the capillaries immediately finds its way into the alveolar spaces. Because the fluid is rich in protein, it coagulates during the preparation of the sections, and is seen in hematoxylin-eosin preparations as pink-stained substance filling out the affected alveoli. Within it are vacuoles due to air bubbles. The fluid contains varying numbers of blood and alveolar cells, but in non-inflammatory edema these are usually not numerous. When the alveoli are distended by the edema fluid, the interalveolar septa are compressed and the capillaries collapsed." ⁸

During the attack there is usually emphysema, either temporary or an accentuation of a previously existing condition. The diaphragm is low, and the thorax is held in the position of full inspiration. Clinically, there is hyperresonance, increased antero-posterior diameter of the chest, diminished breath sounds, partial or complete obliteration of the absolute cardiac dullness and diminished movements of the diaphragm. The increased thoracic volume is occupied partly by increased amounts of blood in the vascular bed of the lung, partly by transudation of edema fluid into the pericapillary and intra-alveolar space and probably by an increase in the total volume of free air space.⁹

Parker and Weiss¹⁰ have distinguished between pericapillary edema and intra-alveolar edema and demonstrate that one may occur without the other. They feel that this may account for the lack of correlation between dyspnea, on the one hand, and clinical signs such as pulmonary râles, on the other hand, in certain cases of heart failure. They show that without edema fluid within the alveolar space there may be edema in the alveolar wall and

interlobular septa with increased amounts of collagen and thickening of the alveoli. These may contribute to the "Lungenstarre" (stiffening of the lungs) described by von Basch.¹¹ It is an interesting hypothesis that some similar change may be found in the type of case described here. We plan to examine the smaller bronchioles of patients who may die in asthmatoïd heart failure without basal râles to determine if their walls contain edema without free fluid within the lumina. It is possible of course, as in the case of allergic asthma, for exudate in the bronchioles to produce wheezing râles by narrowing the air passages. This is undoubtedly the mechanism in those patients showing basal râles as well.

Three cases have been selected from among our case histories to illustrate several phases of the problem. Each case has a brief comment, and a consideration of differential diagnosis will follow in a separate section.

CASE REPORTS

1. *Left Ventricular Failure Simulating Allergic Asthma.* M. M., a married Italian woman of 33, was admitted to the service of Dr. Tasker Howard in a paroxysm of dyspnea with the diagnosis of bronchial asthma. For several months there had been intermittent difficulty in breathing and the subjective sensation of "wheezing." There was no past or familial history of allergic disease. The lungs, according to the note of the admitting physician, showed "typical signs of bronchial asthma," sibilant and sonorous wheezes scattered evenly throughout both lungs, anteriorly and posteriorly. There were no moist or basal râles. Expiration was prolonged throughout. There were no clinical signs of right heart failure such as hepatic enlargement or peripheral edema but the presence of mitral stenosis led to further investigation of the cardiac status. On close questioning, the patient admitted the presence of increasing orthopnea and of dyspnea on exertion during the period covered by her chief complaint. The wheezing was worse at night and with the patient recumbent. Further examination revealed a venous pressure of 15 cm. of water and indirect evidence of increased pressure in the pulmonary circulation: accentuation of the pulmonary second sound, increase in the size of the pulmonary conus and roentgen-ray evidence of passive congestion in the lungs. The electrocardiogram showed right axis deviation. The circulation time (cyanide method) was 34 seconds; the ether time (arm-to-lung method of Hitzig) was 10 seconds; the "left heart" time (by subtraction) was 24 seconds or markedly prolonged. Adrenalin gave moderate transient relief but improvement was striking only after treatment directed toward correction of the cardiac failure, digitalization, sedatives, rest and fluid restriction. The patient was discharged 10 days later much improved and with no asthmatoïd signs in the chest.

Comment. A case closely simulating allergic asthma even with respect to relief with adrenalin. It is somewhat unusual in that the asthmatoïd dyspnea followed mitral stenosis. Most cases of this type occur in the course of hypertensive heart disease. It should be noted of course that the administration of adrenalin to a patient in cardiac failure may not be without considerable danger.

2. *Allergic Asthma with Incidental Heart Disease.* Y. B., married white Jewess of 59, was admitted to the service of Dr. Tasker Howard during a paroxysm of dyspnea, the lungs showing signs identical with those of case 1. There was a

complaint of wheezing respirations and "choking spells" occurring especially at night for the past year. The past history was completely negative for allergy but a brother and two children have hay fever. The temperature on admission was 101.4° and the leukocyte count was 17,400 with 7 per cent eosinophiles. The blood pressure was 140 mm. of mercury systolic and 80 diastolic, the pulse 120 and regular. The heart was not enlarged and showed no murmurs. The venous pressure during the paroxysm was 22 cm. of water, subsiding thereafter to the normal level of 7.8. The circulation time was 15.0 seconds and the ether time 7.0 seconds, both normal. There was striking relief with adrenalin but before admission the patient had been told that she had cardiac asthma and was advised against the use of adrenalin. The electrocardiogram showed a right bundle branch block.

Comment. The diagnosis here was not easy during the paroxysm. Abrupt onset of allergic asthma is very unusual at the age of 58 and the increased venous pressure and electrocardiographic changes suggested heart disease. However, the positive family history, the eosinophilia, the lack of any evidence of congestive failure, the lowering of the venous pressure after the paroxysm, the precipitation of the attacks by bouts of febrile bronchitis, the normal circulation time all establish the diagnosis of bronchial asthma. The patient was treated on this basis and was discharged relieved.

Allergic asthma appearing late in life may simulate heart disease. Electrocardiographic findings indicated myocardial damage which had no relationship to the attack. Prompt response to adrenalin is somewhat in favor of allergic disease but not conclusive. Note that the paroxysms occurred especially at night as in case 1 and that the venous pressure was elevated when first taken.

3. *Left Ventricular Failure in a Patient with Allergic Asthma.* H. V., a married American man of 55, was admitted to the service of Dr. Carl H. Greene during a bout of dyspnea. The physical findings in the lungs were identical with those found in the first two cases. The patient had a long standing glomerulonephritis and hypertension and signs of both right and left heart failure without, however, basal râles. The cyanide and pulmonary circulation times were both prolonged, 31 and 17 seconds respectively. The patient responded promptly to morphine, digitalis, and venesection. There was an eosinophilia of 9 per cent and some persistence of sibilant râles after the cardiac failure was improved. It was then discovered that the patient was a furrier with long standing allergic asthma for which he had been treated and for which he had positive skin tests.

Comment. As in this case, a patient with allergic asthma may develop left ventricular failure.¹⁸ When in doubt, it is better to treat both conditions. Increased pulmonary pressure may increase the asthmatic signs and symptoms of allergic asthma. Finding all the criteria of true bronchial asthma should not rule out heart failure.

DIFFERENTIAL DIAGNOSIS

Blood Count. Eosinophilia is a clue to the diagnosis of bronchial asthma but it may occur in other diseases or in a complicating heart failure. Polycythemia is often present secondary to the pulmonary changes of either disease and is not diagnostic.

Roentgen-Ray Diagnosis. Roentgenography, while useful, is rarely conclusive. Infarcts, bronchopneumonia patches, pleural effusions, effusions into the interlobar spaces are often found but these cases rarely present difficulties in differential diagnosis. The hilar shadows are usually enlarged, sometimes to a very marked degree. There is sometimes a fanlike radiation toward the periphery and particularly toward the base of the lung. Pezzi¹² has termed the expansile pulsation of the hilar shadows occasionally seen in left heart failure the "hilar dance." All increases in hilar shadow usually decrease with response to therapy. The lung markings are increased in left heart failure and are sometimes difficult to distinguish from bronchopneumonia. The lung fields in cases of pulmonary engorgement appear denser than usual. Fluoroscopically, markedly diminished excursion of the left ventricle contrasting vividly with good excursion of the right cardiac border may be seen in the left oblique position.⁹

Examination of the Heart. This need not be discussed in detail. The findings are those of the underlying heart disease, usually hypertensive heart disease although occasionally rheumatic endocarditis as in our first case. The pulmonic second sound may be sharply accentuated because of the increased tension in the pulmonary circulation. The heart sounds may be poor but are sometimes surprisingly good. The accompanying emphysema, whether temporary or permanent, usually precludes accurate percussion. Palpation of the apical impulse may help in determining the size of the heart.

Physical Signs in the Lungs. If basal râles or signs of effusion are present, the diagnosis of cardiac asthma may be fairly easy. In the group of cases under discussion, a small percentage of the total number of cases of left ventricular failure, the signs may be indistinguishable from those of allergic asthma with accompanying emphysema. The diaphragm is low, expiration is prolonged, the chest is held in an inspiratory position, the percussion note is hyperresonant, there is no post-expiratory pause and scattered throughout both lungs, front and back, are sibilant and sonorous râles and rhonchi. Note should be made here of the occasional case of left ventricular failure without râles of any sort in whom the only lung signs are those of rapid respiration, usually with cyanosis and transient emphysema.

History and Response to Adrenalin. A positive history for allergic conditions in the patient or his family or of a satisfactory response to adrenalin is not, as we have seen, adequate evidence that the attack is not cardiac in origin. Onset in late life and nocturnal incidence of dyspnea favor heart failure but are not conclusive as was shown in case 2.

Venous Pressure Determinations. These have been proposed to distinguish between cardiac and bronchial dyspnea. It is true that if the patient can be put under basal conditions, the venous pressure is usually normal in bronchial asthma in contrast to the elevation in right heart failure. There are two drawbacks to the use of this method, first, that there are occasional cases of isolated left heart failure in which the venous pressure may not be elevated and second, that during an acute paroxysm which is the time

when differential diagnosis is most difficult the venous pressure of the asthmatic is usually sharply elevated no matter what the cause. We have not felt that the venous pressure is of much value in diagnosis during an acute paroxysm.

Circulation Times. Measurement of the circulation time was found to be the most satisfactory method of differential diagnosis. During left ventricular failure, the velocity of blood flow through the pulmonary circuit is markedly decreased so that total circulation times are increased. Usually there is an associated slowing of the stream in the systemic circuit as well, so that the arm-to-lung times are increased thus prolonging still more the total time. In unusual cases, there may be isolated left heart decompensation so that the arm-to-lung time is normal and the total time increased. Following the lead of Oppenheimer and Hitzig,¹³ we have found that measurement of blood velocity has been exceedingly useful in the diagnosis of cardiac asthma and we have been able at the Kings County Hospital to confirm their results. Our methods differed slightly in that we used sodium cyanide¹⁴ for measurement of the total circulation time in place of saccharin. Calcium gluconate and saccharin were used in a few cases but we have felt that the cyanide method gives a sharp end-point, does not depend on a subjective reaction and is more satisfactory in the acutely ill patient. The figures obtained with any of the three measures check closely with one another. For the arm-to-lung time we have used the ether method of Hitzig¹⁵ which we have found fully satisfactory. 0.3 c.c. of ether and an equal amount of physiological saline were injected rapidly into an arm vein and the length of time elapsing until the ether vapor is perceived in the patient's breath was measured. The "left heart" time is obtained by deducting the ether time from the cyanide time.

The total circulation time in 37 cases of bronchial asthma was found to be within normal limits or somewhat decreased. When measurements were taken during a severe paroxysm (the period during which it is necessary to differentiate heart failure) the rate in one-third of the cases was appreciably increased. This increase in blood velocity is undoubtedly due to the fact that the patient is straining during a paroxysm and is not under basal conditions. It will be seen, therefore, that the error introduced into the test by reason of the fact that the subject has not been resting and is not under basal conditions is in the direction of making the venous pressure less sensitive as a differential diagnostic point and of making the circulation time a more sensitive test in that it accentuates the differences in blood velocities in bronchial and cardiac asthma.

There were 49 cases of left ventricular failure observed during the time in which these tests were made. Forty showed basal râles and nine showed signs of asthmatoïd failure, the type of case, namely, which is under primary discussion in this paper. All nine cases showed decreased blood velocity both total and pulmonary. Of the other 40 cases, in one a satisfactory end-point was not established, in three all three circulation measurements

were normal, and in 36 the total circulation time was prolonged. In all 36 the "left heart" time was prolonged and in 21 the arm-to-lung time was prolonged. There were, therefore, 15 cases of isolated left ventricular failure and, if to these the nine cases of asthmatoïd failure are added, there are a total of 24 cases of left ventricular failure without demonstrable involvement of the right heart. These figures are shown in table 1.

TABLE I
Circulation Times in 49 Cases of Left Ventricular Failure with Wheezing Respiration
as Dominant Physical Sign

		Total Time (cyanide)		Pulmonary Time*	
		Normal	Prolonged	Normal	Prolonged
Unsatisfactory endpoint	1				
Isolated left vent. failure	24				
Rt. plus left vent. failure	24				
"Asthmatoid failure"					
(Wheezing resp., no basal râles)	9	0	9	0	9
Left vent. failure with basal râles	40	3	36	3	36

* Obtained by subtraction of ether time from cyanide time. 24 cases of the total series showed normal ether times. This is referred to also as the "left heart" time. A more recent method of estimating this time is described by Gubner, et al.¹⁹

In 11 cases in which there was improvement in symptoms following digitalization, the circulation times were repeated where previous readings had indicated failure of the left ventricle alone. In nine of these cases there was a prompt improvement in the pulmonary blood velocity paralleling closely the clinical improvement although in only three did the circulation time return to normal or less by the time the patient was ready to get out of bed. In two other cases of the eleven there was also an improvement in the circulation time, but this lagged considerably behind the clinical improvement. These findings confirm our clinical opinion that failure of the left heart responds approximately to the same measures, digitalis, etc., to which right heart failure responds. No special effort was made to assess the value of venesection in improving the blood velocities. These findings, with respect to the effect of digitalis, and in general the other findings mentioned in this section of the paper confirm the findings of Hitzig, et al.¹⁶ reported in their excellent study in 1935.

COMMENT

Wheezing respiration is commonly found in heart failure and may indeed be the only physical sign present in the lungs, occurring without the basal râles usually present in heart failure. In rare cases, rapid breathing may be the only physical sign in left heart failure. Wheezing decompensation, especially in the type in which there are no basal râles and designated

as "asthmatoïd heart failure" in this paper, are sometimes distinguished only with great difficulty from bronchial asthma. This is especially true in those cases of bronchial asthma in which there are moist as well as wheezing râles or in which there may be some degree of right heart failure.

The pathogenesis of wheezing respiration in heart failure is discussed in the body of the paper and it is suggested that, as in allergic asthma, narrowing of the lumina of the smaller bronchi and bronchioles may be caused by spasm, exudate and edematous involvement of the walls in varying degrees.

Case histories illustrating certain aspects of the problem are given and other cases in the series are analyzed in two tables. The differential diagnosis is discussed in some detail and it is reëmphasized that by physical examination and response to adrenalin it may be impossible to distinguish between cardiac and allergic asthma during, or shortly after a paroxysm. Measurement of the venous pressure is not considered an adequate differential diagnostic point.

TABLE II
Classification of Cases According to Primary Diagnosis

	Isolated Left Failure		Combined Right and Left Failure
	Without	With	
	Basal Râles		
Rheumatic endocarditis	3	2	11
Mitral stenosis	1	2	2
Aortic insufficiency	1		3
Aortic stenosis			1
Combined aortic and mitral	1		5
Syphilitic heart disease	1	1	2
Chronic glomerulo-nephritis	1	2	3
Hypertensive heart disease	3	9	6
Coronary disease	1	1	2

Following the work of Hitzig, King, Fishberg and Oppenheimer, it was found that circulation times enabled us to diagnose cardiac asthma rapidly. Arm-to-lung (ether), arm-to-carotid (cyanide), and pulmonary circuit times were utilized. In many cases, left ventricular failure was accompanied by some degree of right heart failure but in some cases there was isolated left-sided decompensation. In most cases digitalis increased the velocity of blood flow through the pulmonary circuit just as it increases the blood velocity in the systemic circuit in right heart decompensation.

CONCLUSIONS

1. Wheezing respiration is common in left ventricular failure. It may occur without basal râles ("asthmatoïd heart failure") in which case it closely simulates allergic asthma in symptoms, physical signs and response to adrenalin.

2. The pathogenesis is discussed and illustrative cases given.

3. The quickest and easiest method of determining whether or not a case of paroxysmal dyspnea is cardiac in origin is by means of a study of the circulation times which show decreased blood velocity in the pulmonary circuit. Arm-to-carotid (cyanide) and arm-to-lung (ether) times may be quickly and accurately determined at the bedside. They are more reliable in the differential diagnosis than determinations of the venous pressure.

BIBLIOGRAPHY

1. COCOA, A. F., WALZER, M., and THOMMEN, A. A.: Asthma and hay fever, 1931, Charles C. Thomas, Springfield.
2. LAMSON, R. W., and BUTT, E. M.: Fatal "asthma," Jr. Am. Med. Assoc., 1937, cviii, 1844.
3. OLD, HERBERT: Asthma from the life insurance standpoint, Jr. Allergy, 1933, iv, 122.
4. DUBLIN, L. I., and MARKS, H. H.: Mortality of risks with asthma, quoted in Lamson and Butt.
5. An interesting defence of the use of "cardiac asthma" is to be found in the opening paragraphs of:
PRATT, J. H.: Cardiac asthma, Jr. Am. Med. Assoc., 1926, lxxxvii, 809.
6. MACKENZIE, J.: Angina pectoris, 1923, Hodder and Stoughton, London.
7. EPPINGER, H., VON PAPP, I., and SCHWARZ, H.: Ueber das Asthma cardiale, 1924, Berlin.
8. FISHBERG, ARTHUR M.: Heart failure, 1937, Lea and Febiger, Philadelphia.
9. WEISS, S., and ROBB, G. P.: Cardiac asthma, Jr. Am. Med. Assoc., 1933, c, 1841.
10. PARKER, FREDERIC, JR., and WEISS, S.: The nature and significance of the structural changes in the lungs in mitral stenosis, Am. Jr. Path., 1936, xii, 573.
11. VON BASCH, S. S. K.: Allgemeine Physiologie und Pathologie des Kreislaufs, 1892, Vienna.
12. PEZZI, C.: The radioscopic sign of the "hilum dance," Libman Anniversary Volumes, 1932, iii, 931, New York.
13. OPPENHEIMER, B. S., and HITZIG, W.: Circulatory measurements in chronic lung disorders, Am. Heart Jr., 1936, xii, 257.
14. ROBB, G. P., and WEISS, S.: Method for measurement of pulmonary and peripheral venous blood flow in man, Am. Heart Jr., 1933, viii, 650.
15. HITZIG, W.: Measurement of circulation time from antecubital veins to pulmonary capillaries, Proc. Soc. Exper. Biol. and Med., 1934, xxxi, 935.
16. HITZIG, W., KING, F. H., and FISHBERG, A. M.: Circulation time in failure of the left side of the heart, Arch. Int. Med., 1935, lv, 112.
17. NORRIS, G. W., and LANDIS, H. K. M.: Diseases of the chest, 1933, W. B. Saunders Co., Philadelphia.
18. A good discussion is to be found in: SWINEFORD, O., JR., and MAGRUDER, R. G.: Asthma in heart disease, South. Med. Jr., 1937, xxx, 829.
19. GUBNER, R., SCHNUR, S., and CRAWFORD, J. H.: The use of CO₂ inhalation as a test of circulation time, Jr. Clin. Invest., 1939, xviii, 395.

SUGGESTED REVISIONS OF MEDICAL PHARMACOLOGY *

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THE recent cure of general bacterial infections with drugs of the sulfonamide group should bury forever the belief that treatment by drugs can be palliative only. It might seem, therefore, that this were as inopportune a time as could be chosen to speak of the failure of pharmacology and to consider reorganization. Science, however, does not progress entirely by revolutionary discoveries, and, although the cure of infections by drugs undoubtedly will stimulate interest in pharmacology for a time, the widespread dissatisfaction which exists will become evident again if there is any fundamental cause for it. It would, therefore, seem well to discover, if possible, why it is that Dr. William D. Cutter, Secretary of the American Medical Association Council on Medical Education and Hospitals, in a recent public address,¹ stated that pharmacology should be either discontinued or reorganized; why it was that the pharmacologists of this country, as well as of Europe, recently met to discuss their difficulties; why two of our newest and most highly endowed schools of medicine failed to provide separate departments of pharmacology; and why others have spent several years trying to decide whether to drop the subject, combine it with physiology or biochemistry, or replace it by a therapeutic institute with a clinician at its head. Well over one hundred articles on the status of pharmacology, materia medica, and therapeutics may be found in the literature,²⁻⁵⁵ among which those by Griesinger,² Küchenmeister,³ Fraser,⁴ Beyer,⁵ Jerome,⁷ Abel,¹⁰ Hill,¹² Sollmann,¹³ Cushny,²¹ Edmunds,²⁷ Dixon,²⁸ Bierring,³⁰ Handovsky,³¹ Meyer,³² Jarisch,³³ Clark,³⁴ Edmunds,³⁸ Starkenstein,⁴⁰ Seel,⁴⁷ DeGraff,⁴⁹ Edmunds,⁵⁰ Hayman,⁵¹ Heubner,⁵² and MacNider⁵³ are of particular interest. No conclusions seem to have been reached other than that pharmacology has not received the proper support. The present situation is an anomalous one. Everyone wants to know more pharmacology, all admit that some of the best men are in this field and that their work is of the highest type, and yet dissatisfaction with this subject is very prevalent.

Several years ago a note was published by the present author,⁵⁶ suggesting a fundamental cause of our difficulties, which could be remedied by simple means. The cause was considered to be that pharmacologists are not studying the human organism as are all others in medicine, but they are, at least by definition, studying drugs and their actions. The difference between studying the reaction of the organism to drugs and the "action" of drugs on the organism may seem of little importance or nonexistent. It is,

* Read at the New Orleans meeting of the American College of Physicians March 30, 1939.

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however, the object of this communication to show how fundamental this difference is; to urge that we give up once for all the study of drugs and their actions, which, in spite of anything to the contrary, is pharmacy, and develop a medical science, the object of which is the study of the human organism by means of its reaction to chemical substances, a systematic method for doing which is described. Before taking this up in detail, it might be well to consider briefly what we mean by pharmacology, as well as its relation to other branches of medicine.

BUCHHEIM'S PHARMACOLOGY

When magic was supposed to reside in drugs and cause the remarkable disturbances seen in man when these were taken by him, it was a scientific procedure to examine all manner of plants for such magical actions. Later it became equally, if not more, interesting to discover what this magic was which drugs contained. When, however, through such studies the science of chemistry was developed and it was found that the magic consisted of chemical molecules, the interest and science of the study of drugs were gone, and pharmacy, the father of all science perhaps, became an art, and plant and animal tissues no longer had any interest as such to the pharmacists but merely as sources of chemical substances which had, or might have, "actions" in man.

In the middle of the nineteenth century *materia medica*, the remnant of pharmacy left in our schools of medicine, was a chaos of fact and fancy. Schmiedeberg⁵⁷ gives a very graphic description of it: "What at that time under the name of *materia medica* existed as a medical discipline could hardly be spoken of as a science. Its contents consisted of a massive sum of experience and of minutely described directions and rules for the use of an infinite number of drugs and preparations, of which the action and use in sickness was based on intuition and assumptions which owed their origin to the dogma of natural philosophy."

The fearful task of separating from this confused mass of data that which had some probability of factuality and that which was purely speculative was undertaken by Rudolf Buchheim in Dorpat. Buchheim was a great scholar, not only in the languages, but in chemistry, physiology, pharmacy, botany, and medicine. He was editor-in-chief of the *Pharmaceutischen Centralblattes*, which later became the *Chemisches Centralblatt*. He also supplied the reports of physiological chemistry in Schmidt's *Jahrbüchern der Medicin*. He was an active investigator. Four years spent in translating and reorganizing the 1,700 pages of Pereira's "Handbuch der Arzneimittellehre" showed him the need for a different way of dealing with drugs in medicine.

Although individuals in France, England, and Germany had experimented with drugs on animals, it was Buchheim who recognized the necessity for a systematic attack on the problem in order to discover how drugs act. In his own house, with his own money, Buchheim established the first

pharmacological laboratory for the experimental study of the action of drugs. This laboratory was later taken over by the University of Dorpat and Buchheim's title changed from that of Professor of *Arzneimittellehre*, *Diätetik und Geschichte und Encyclopädie der Medicin*, to Professor of Pharmacology. Pharmacology from *φάρμακον*, a drug, and *λογία*, speak, was defined as the study of drugs and their actions. Pharmacology is, however, an old word used since 1720 synonymously with pharmacy.

Buchheim was much impressed by the need of system if one wished to develop a science rather than accumulate a mass of unorganized information. He devised a system, partly chemical and partly biological, for the classification of medicinal agents and their "actions" in the body, which was set forth in three editions of his "*Lehrbuch der Arzneimittellehre*." ⁵⁸ Although Buchheim was apparently intent on the need of order and system, he failed to make his a truly systematic classification. His group of drugs brought together under the heading "*Glaubersalzes*" cannot be considered a group of substances related in any way chemically to Glauber's salt, but a heterogeneous collection of substances which have as their one common property an ability to produce catharsis.

VIII. Gruppe des Glaubersalzes

Glaubersalz
 Bittersalz
 Schwefelsaures Kalium
 Phosphorsaures Natrium
 Weinsaures Kalium
 Seignettesalz
 Abführendes Brausepulver
 Borazweinstein
 Aethylschwefelsaures Natrium
 Doppeltkohlensaures Magnesium
 Citronensaures Magnesium
 Mannit, Manna, Mannasyrup

Thus, we find at the very beginning of "Pharmacology" that although Buchheim made a contribution of enormous importance to medicine, he offered no solid foundation on which a new medical *science* could be built. Supposing the active principle of every plant, herb, and animal extract were known in pure chemical form and that these, as well as the several hundred thousand other chemical substances, had been arranged strictly according to some systematic chemical nomenclature, what use would such a classification be to medicine? If one did not know his pharmacology, how could one find an anesthetic, cathartic, or anthelmintic by looking in such a systematic, alphabetical list, an example of which is given below, taken from Dyson's "*The Chemistry of Chemotherapy*." ⁵⁹

α : α' -Dichloroisopropyl alcohol carbamic ester
 3: 5-Dichlorophenyl arsonic acid
 3: 8-Diethoxy-9-carboxylic acid
 Diethylacetamide

Diethylamine
 Diethylaminoacetonitrile
 Diethylaminolactic nitrile
 Diethylaminolactic nitrile methyl iodide
 Diethylaminophenylacetonitrile
 Diethyl aniline
 Diethyl carbinol
 1:1'-Diethylcarbocyanine iodide
 Diethyl ether
 Diethylglycine-p-amino-o-oxybenzoic acid methyl ester

Consider also our pharmacopoeia, which is arranged in the same manner. No one can use it without a previous knowledge of pharmacology. This is being recognized by the pharmacopoeial committee, which has issued a small booklet grouping the pharmacopoeial preparations under such headings as cardiac drugs, cathartics, antiseptics, anthelmintics. Furthermore, one cannot compare the "actions" of two or more drugs. How can the increase of blood pressure and respiratory rate produced by one substance be compared with the uterine contractions and diuresis produced by another? It is questionable if Buchheim's pharmacology allows the systematic treatment necessary for the development of a science.

The Error in Buchheim's Pharmacological Concept. Buchheim's first pupil was Otto Schmiedeberg, who, spared from the drudgery of reorganization and systematization and equipped with his splendid laboratory in Strassburg, stepped into this untouched field of pharmacology, free to carry on Buchheim's teachings. That he was well fitted for this opportunity was shown by the impetus which he gave to this subject and the founding of over 40 new departments in different parts of the world by his pupils, among whom were leaders in the medical profession. Pharmacology was greeted with a surprising wave of enthusiasm, but, even with the great productivity of these laboratories, doubt began to arise as to the status of pharmacology, and, in spite of all attempts to quell such fears, this doubt still exists.

Although Buchheim's emphasis on the experimental investigation of drugs and the need of system should receive nothing but praise, if we look at the matter without sentiment, it will be found that pharmacology differed in no way from pharmacy. The only way the pharmacist had to differentiate a "drug" from any other plant was to study its "action" in man or animals. True it is that these studies were not systematic, but the action in man of a great many drugs was known to us before Buchheim's time and much experimental work on the action of drugs in animals had been carried out in different laboratories. There was, therefore, nothing essentially new in the concept of pharmacology nor in its name. There was, however, the idea of systematizing our knowledge of the "action" of drugs, but this system failed even in Buchheim's own hands and that it was given up by his followers can be seen from the following brief review.

Schmiedeberg recognized that Buchheim's system and classification was impractical as well as unscientific. He was, however, unable to devise a

systematic classification of his own and, on this account, gave up a life-long desire to write a systematic textbook on pharmacology, publishing instead his "Grundriss der Pharmakologie"⁶⁰ for the aid of medical students and practitioners.

An analysis of the tables of contents of Schmiedeberg's book and those of his followers shows one common tendency, that is, to turn from Buchheim's idea of chemical headings to biological ones. The first chapter in Schmiedeberg's book, for example, is headed "The Nerve and Muscle Poisons"; the second, "Organic Substances Causing Local Irritation." Brunton,⁶¹ although his book is a model of system of a sort, apparently realized the impossibility of a systematic chemical approach to the subject and went at it from all sides—chemical, botanical, zoölogical, pharmacological, and therapeutic. Meyer and Gottlieb's splendid book⁶² is based entirely on a biological plan; in fact, they open their introduction to the first edition as follows: "Experimental pharmacology in the broadest sense deals with the reactions of living organisms to chemical substances or, to put the matter in another way, the behavior of organisms to changes in the chemical environment in which they live. Pharmacology is a part of Biology." They use, however, the same general mixture of tissue, organ, and function headings as did Schmiedeberg and Brunton. Sollmann,⁶³ who has perhaps done as much for pharmacology proper as anyone in this country, follows no systematic plan whatever, pharmacological, chemical, botanical, medical headings being used in no particular order—"The Pharmacology of Temperature Regulation," "Antimony," "Uranium," "Agranulocytosis," "Allergic Phenomena," and so forth. *We may safely conclude that after nearly one hundred years of pharmacology, there is no evidence of the "system" which Buchheim felt so necessary.* His idea of a systematic arrangement of drugs, under which one was to find their "actions," has gone almost entirely, and one finds instead that the pharmacologist is arranging drugs under some part or function of the body.

The Functions of a Pharmacologist. We have considered Buchheim's pharmacology, and with this in mind let us see what are the functions of a pharmacologist. These are set forth in a great many articles, but a brief outline of the table of contents of Sir Thomas Lauder Brunton's classical volume on "Pharmacology, Therapeutics, and Materia Medica"⁶¹ will show them sufficiently well for our purpose. One cannot but marvel at the extent of Brunton's knowledge.

Brunton begins with a description of the chemical elements, their classification, and the general reactions between chemical substances and the body. He then goes on to the action of drugs on protoplasm, blood, and low organisms, moving on to their actions on higher invertebrates. After this, the actions of drugs on various parts of the body are taken up, such as those on muscle, nerve, spinal cord, brain and organs of special sense, and on functions as respiration. He then includes a chapter on methods of administering baths of all types, as well as massage, the stomach pump, and so forth.

After this, antidotes and antagonistic action of drugs are taken up. Then, under "Section II, General Pharmacy" we find all the pharmaceutical preparations; after this, a systematic survey of drugs in two parts: "Inorganic Materia Medica"—hydrogen, oxygen, sulphur, acids, metals, and so forth—arranged in a very systematic manner, and "Organic Materia Medica"—carbon compounds, fatty acid series, and aromatic series. This is followed by several chapters on "Vegetable Materia Medica," systematically arranged in "Sub-Kingdom I., Phanerogamae. Division I., Angiospermae; Class I., Dicotyledones Polypetalae; Sub-Class I., Thalamiflorae," and so forth. The animal kingdom is treated with equal care—classes of "Mammalia," "Aves," "Pisces," and orders of "Rodentia," "Pachydermata" under which comes "Lard." An index of diseases and remedies concludes the book. Here we find "Abscess" treated by alcohol, iodine, oakum, sheet lead, sodium auro-terchloride. The list includes all manner of diseases and symptoms, as acidity, acne, afterpains, and their treatment. If we add to this list serums, vaccines, pollens, vitamins, roentgen-rays, radium, and ultra-violet light, and, as some would have us, the hospital pharmacy, as well as a ward, the list is certainly formidable.

In view of the above, the following quotation from a letter to Professor Heubner seems particularly apt. This was written in 1938 by Sir Henry Dale, who has kindly given me permission to use it. "In general terms, the question I raised was the necessity of discussing, *not* the necessity for pharmacologists, but the proper claims and the proper scope of Pharmacology, in view of the rapid changes already in progress in the aims and methods of therapeutics, and of the accelerated changes which I think can be foreseen in the near future. Unless something is done, the impression will grow, that Pharmacology is only a nebulous border-line between Biochemistry, Physiology, and Pathology, on the one hand, and Therapeutics on the other. My aim is certainly not to extinguish the Pharmacologist, but to secure his survival."

After the statements of Schmiedeberg, Meyer, Cushny, Dixon, and others that we are studying the "reaction of the organism to chemical substances," and the fact that whatever system there is in pharmacology does not use drugs as a basis, but some part or function of the organism, have we not already given up pharmacy or its analogue, pharmacology, and are we not in reality studying the organism rather than drugs?

The "Action" of Drugs versus the Reaction of the Organism to Drugs. In order to settle this philosophical question, it will be necessary to digress somewhat. We will assume that all things are of chemical nature, that they are made of two things only, electrons and protons, and that they differ only in the number and arrangement of these.

We will also consider for the sake of argument that drugs consist of single, pure, chemical substances. A drug is not a magical substance. We can never see a molecule, but we know it only by its reactions to other chemical substances. Its actions can, therefore, be nothing but its chemical

or physical properties or functions. These are fixed at the beginning by the number and arrangement of its electrons and protons. A drug's actions or reactions, behavior, or what one wishes to call it, in a test-tube reaction with other chemical substances, in the body of a man, turtle, or fish, is preordained; it is nothing but a chemical reaction (or a physico-chemical one) and could be predicted by a perfect chemist if he could know the chemical environment into which this substance was to enter. If his drug were hydrochloric acid and the chemical environment silver nitrate solution only, any high school student could predict the reaction. If, however, the drug were a complex organic substance about to enter even a test tube full of other organic substances, our best chemist would be utterly unable to predict what would happen, but merely from lack of knowledge. The theoretically perfect chemist could make such a prediction.

When we put a drug into a living organism, what are we doing? We start with a substance about which we supposedly know everything (which practically never is the case), and we put it into an almost limitless sea of chemical substances, many of utterly unknown nature. As we know our drug, our main interest lies in the unknown, that is, the human organism. We observe some response, as a change in rate of the animal's respiration. No one would dispute that this is the result of injection of the drug, but is it the "action" of the drug? I think not. The drug first came in contact with a certain chemical environment in the blood, certain cells, or body fluids. It reacted with one or more chemical substances of this environment or by its presence brought about a physico-chemical change in the environment, which in our present state of knowledge we are seldom able to unravel. This primary reaction was a purely chemical or physico-chemical one. It would have occurred anywhere, in any test tube or animal's body with exactly the same setup of chemical substances. The secondary changes, however, leading to nerve impulses, muscle contractions, and so forth, although of a chemical or physico-chemical nature, were not necessarily reactions with the drug but were due to *the specific chemical setup in this particular species of organism*. This particular architectural arrangement of chemical substances can be found nowhere else, except in another individual of the same animal species. Although everything that we know of must be of a chemical nature, as it is made of electrons and protons, the properties and functions of any specific organized group of chemical substances are dependent upon the architectural arrangement of the molecules of this group exactly as the properties and functions of a molecule are dependent upon the architectural arrangement of its atoms. A pig, a cow, and a bird might conceivably be made of the same chemical substances, but their number and arrangement give these particular agglomerations of electrons and protons properties of their own.

It is hoped that this illustration will be sufficient to make it clear that we are not studying drugs, as Buchheim realized. Their study is chemistry, pharmacy, or materia medica. We are not studying their "actions," which

apparently was not recognized by Buchheim, as their actions are chemical attributes of the drugs and belong in the field of general chemistry. We are instead studying the unknown, the human organism, a particular, complex agglomeration of chemical substances, and using chemical substances as tools with which to do this. One more illustration may be allowable.

$$Q \rightleftharpoons \begin{cases} A = \text{Color reaction} \\ B = \text{Precipitate} \\ C = \text{Formation of substance } x \text{ of known structure} \\ D = \text{Formation of substance } y \text{ of known structure} \\ E = \text{Formation of substance } z \text{ of known structure} \end{cases}$$

When one makes or discovers a new chemical substance, Q , in determining its composition and structure, one does not merely look at it, but arrives at a knowledge of its nature by *allowing it to react with known chemical substances*, as A, B, C, and so forth. By means of such reactions as in-

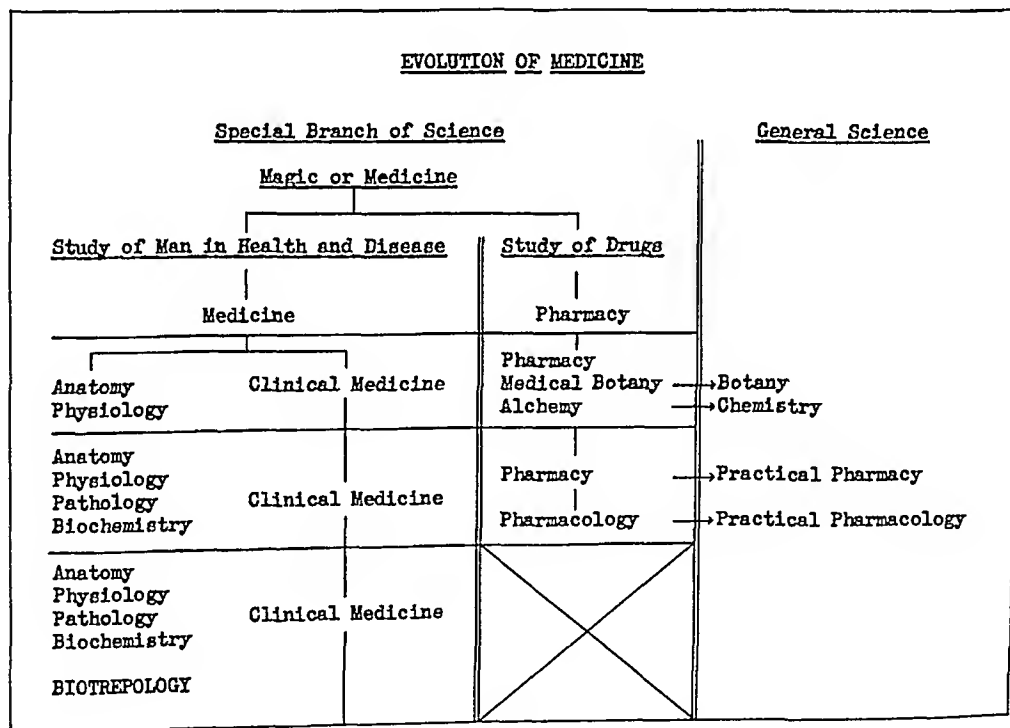


FIG. 1.

indicated above, one determines the character of the unknown substance, the structural arrangement of the different radicals, and so forth.

The age-old reactions between drugs and the body may be looked at in the same light. At first the body was used as a means of differentiating a drug from an inactive plant. Then chemistry was developed; drugs and chemical substances became the *known factors*, and now we are studying the body by means of its reaction to these known chemical substances.⁶⁴

It is a method of unbelievable usefulness. By exposing the body to these substances, we will discover varieties of cells of which we are unaware. We will discover unknown functions of these, and finally those chemical substances of which the cells are built, as well as their ultra-microscopic arrangements. Such knowledge, arrived at by studying the reaction of the organism to chemical substances, automatically gives us that for which we are looking with which to build a systematic foundation for therapeutics.

The following diagram representing the evolution of medicine will serve to show how much came from the original "Medicine, Magic, or Pharmacy"; how very soon medicine split into two groups, one studying the body and the other drugs; how, when our knowledge developed, the magic went out of drugs; how they were seen to be chemical substances; and how their study led to the general science of chemistry. It shows the gradual development of the biological group which has ever since the start held together as an entity, simply subdividing into certain branches for convenience. But it is clear that those studying drugs never did belong to this group. Their interests were not primarily biological. One after another they left our medical schools and in many of these today pharmacology is nothing but a myth, having no department of its own, no special group for its study, originating nothing, and parasitically using the work of others as teaching material in order to conform to the insufficient requirements of our class "A" medical schools.

PART II. THE STUDY OF THE ORGANISM BY MEANS OF ITS REACTION TO CHEMICAL SUBSTANCES

In order to carry out such a plan systematically, the organism as a whole, as well as its various parts, must be considered. An outline of the factors involved is given below:

- (1) Whole organism
- (2) Systems, as the circulatory or respiratory
- (3) Organs, as the eye and the spleen
- (4) Unit building blocks of the organism, the cells
 - (a) Structures, as nucleus, mitochondria
 - (b) Systems, as gels
 - (c) Unit building blocks of the cells, that is, molecules
- (5) Extracellular chemical substances
 - (a) Solutions—body fluids, as plasma, cerebrospinal fluid
 - (b) Deposits, as bone, dental enamel
- (6) Pathological tissue

Invading organisms to be considered individually.

Such an anatomical, rather than functional, outline may seem to many a strange basis for this plan, but a careful analysis will show that all function is reaction of some structure, whether of the whole organism, a system, cell, or molecule.

The measureable reactions of the whole organism are relatively few; changes in weight, height, metabolic rate are examples. The reactions of the whole organism occurring after exposure to chemical substances as alcohol, apomorphine, opium, are so complex that they do not allow simple recording as a whole and are usually broken down for analysis and one body function at a time considered. As, however, one will wish to find a description of the immediate as well as delayed response of the entire organism to each substance, these can be described under the *name* of the substance causing the response. The changes which take place in systems, as the respiratory, and in organs, as the eye, are so numerous that it seems unnecessary to treat them systematically. Blood pressure and respiration rate, for example, are changed by practically every known chemical substance. I have collected several thousand such reactions. They are the resultants of many factors. They are, however, facts and may be recorded under the name of the system, organ, or function in an alphabetical index.

Zoölogical Concept of Organism. Breaking down the organism still further, we come to what at first sight seems a very different class of body divisions, that is, the cells. These are the smallest biological units of which the organism is built; certain well-known types have been recognized and generally agreed upon, as nerve, muscle, and glands. It would seem logical as well as feasible to use cells as the basis of our study and to develop a cellular classification. Although general types of cells have long been recognized and much has been written about certain classes of cells, there has, to my knowledge, been no systematic attempt made to arrange the cells of any one species of animal as the zoölogist classifies animals, in phyla, classes, orders, families, and so forth, for purposes of study. The histologist has been interested in the spatial arrangement of the cells of the kidney. The physiologist is interested in the functional systems of the body and wishes to know the electrical diagram of the different nerve-muscle mechanisms, so to speak. When one uses a chemical substance for purposes of study, rather than the microscope or physical stimulation, this reaches at the same moment many types of cells in different parts of the organism. Whole classes, orders, or families of cells, as the case may be, will respond. *We are not, therefore, primarily interested in the geographical distribution of cells, but in the zoölogical classes of cells of which the body is built.* We do not wish to make the same mistake which Pliny did, who classified animals according to their place of abode, as flying animals, land animals, water animals; that is, we do not want to make geographical divisions of cells, as smooth muscle of the eye, the spleen, the vessels of the liver, when they may all be of exactly the same smooth muscle type. The difficulties of zoölogical classification are beautifully described in Hertwig's *Manual of Zoölogy* translated by Kingsley,⁶⁵ from which and other sources it would seem that zoölogical groups are arrived at by using all means at one's disposal—visual, functional, phylogenetical, paleontological, embryological, and so forth—and that the final criterion is the consensus of zoölogical

opinion. It would almost seem that the method adopted by Adam and Eve for naming the animals in the garden of Eden, described to me many years ago by Dr. William T. Councilman, might be the best for classifying and naming the cells of the body. "What shall we call this little thing?" said Eve. "Well, it looks like a toad and hops like a toad. Why not call it a toad?" replied Adam.

The zoölogists deal with individuals which are free to move about. We must deal with cells many of which are fixed in relation to other cells, and it is often difficult to know what is part of one or the other, as is the case with certain nerves and muscles. Then we are well aware that in reality there are no boundaries within the body. We consist of a shell of dead epithelium full of salt solution in which are the body cells, but these cells are chemical agglomerations bounded by chemical membranes and the whole immersed in a chemical solution. The cell is in equilibrium with the solution in which it lives, and so are all the other cells of the body. Thus no cell can exist alone, but is in balance with the rest of the organism. For practical purposes, however, we may consider cells as units. We shall probably do well to make too few rather than too many subdivisions of tissues, but with such fine methods of differentiation as those of reaction to chemical substances, we might almost be able to show that each cell in the body differs from every other. The cell again will be found to have its parts which correspond to the systems and organs of the body, and these are known to be built of molecules, which in turn are made up of atomic systems, below which we need not go.

It is, however, in the cellular units that I believe the greatest progress will be made. We have observed the cells both micro- and ultra-microscopically, and it is doubtful if we can go much further by visual means. However, by applying the methods used by the chemist in determining the invisible composition and structure of molecules, we may possibly discover the components as well as the invisible structure of the cell, as suggested above.

We will make use of every reaction at our disposal, regardless of type, but many of them will be gross reactions of the organism, as convulsions, change in respiratory rate, which can be easily seen; others, the appearance in the blood, urine, or expired air of substances not normally present; still others, intracellular reactions which will take elaborate means for investigation. But even if we cannot describe, after introducing into the organism a few molecules of acetylcholine, just what chemical reaction goes on in certain cells, we eventually discover which cells are primarily affected, and gradually discover a whole series of substances which produce this same response in these particular cells. From such data it is likely that some day someone will solve the riddle and tell us the substance or architectural chemical arrangement within the cell which primarily reacted with these substances to start the observable body response.

Extracellular Chemical Substances. Solutions, as the plasma, bile, cerebrospinal fluid, are not living substances. Many of them, as well as extracellular deposits, can be obtained in large enough amounts for direct chemical analysis. Data concerning changes which occur in such systems when exposed to chemical substances can be recorded under this heading alphabetically.

It is my purpose to point out the immensity of our problem of studying the reaction of the organism to chemical substances rather than with any thought of giving the impression that it is a simple matter. The problem is so great and we are so utterly unprepared for it that anything in the way of an actual proposal will seem absurd. However, a beginning must be made and the following outline will serve to illustrate a few points which will immediately come to mind.

THE HUMAN ORGANISM

I. NEURONS

A. Receptors

1. Olfactory
2. Optic
3. Gustatory
 - a. Of bitter taste
 - b. Of sweet taste
 - c. Of sour taste
 - d. Of salt taste
4. Auditory
5. Proprioceptive
 - a. Vestibular
 - (1) Labyrinthine
 - (2) Of semicircular canals
 - b. Of muscles, joints, and tendons
6. Of tactile discrimination and stereognosis
7. Of coarse touch and pressure
8. Of pain
9. Of temperature
 - a. For heat
 - b. For cold
10. Of visceral reflexes

B. Coördinating Neurons, especially the following groups (including synapses)

1. Of sensation and consciousness
2. Of contraction of skeletal muscle in voluntary movements
3. Ocular
 - a. For accommodation
 - b. For pupillary constriction
 - c. For pupillary dilatation
 - d. For movements of extra-ocular muscles
4. Glandular
 - a. For lacrimation
 - b. For salivation
 - c. For sweating
 - d. For secretion of mucus, digestive juices, etc.

5. Gastrointestinal

- a. For swallowing
- b. For vomiting
- c. For gastric and intestinal motility
- d. For defecation

6. Genito-urinary

- a. For bladder control
- b. For erection and ejaculation
- c. For uterine contraction

7. Cardiovascular

- a. For vasoconstriction
- b. For vasodilatation
- c. For cardiac inhibition
- d. For cardiac acceleration

8. Respiratory

9. Sympathetic regulatory

10. Parasympathetic regulatory

11. Heat regulatory

C. Effectors

1. Somatic (to skeletal muscle)
2. Visceral (preganglionic and postganglionic)
 - a. Craniosacral (parasympathetic)
 - b. Thoracico-lumbar (sympathetic)

II. MUSCLE CELLS

A. Skeletal

1. Muscle fiber (sarcoplasm, myofibrillae)
2. Spindle fibers
3. Myoneural junction

B. Cardiac

1. Auricular
2. Ventricular
3. Nodal
 - a. Sino-auricular
 - b. Auriculoventricular
4. Purkinje tissue

C. Smooth

1. Uterine
2. Vascular
 - Intestinal sphincters
 - Radial of iris
3. Gastrointestinal
 - Gall-bladder
 - Bronchial
 - Fundus of urinary bladder
 - Circular of iris
 - Ureteral

III. GLAND CELLS

A. Externally Secreting

1. Ceruminous
2. Sebaceous
 - a. Of hair follicles
 - b. Of Meibomian glands

3. Serous

- a. Lacrimal
- b. Sudoriparous
- c. Zymogenic
 - (1) Salivary
 - (2) Pancreatic
 - (3) Fundic
 - (4) Of Paneth cells

4. Mucous

- a. Of gastrointestinal tract
 - (1) Salivary
 - (2) Buccal
 - (3) Of sinuses
 - (4) Esophageal
 - (5) Cardiac
 - (6) Pyloric
 - (7) Of Brunner
 - (8) Columnar epithelial
 - (9) Of gall-bladder and ducts
 - b. Of genito-urinary tract
 - (1) Urethral and para-urethral
 - (2) Cervical
 - c. Of respiratory tract
- 5. Of intestinal columnar epithelium (other than serous or mucous)
 - 6. Of mammary gland
 - 7. Renal
 - 8. Hepatic (bile secretory)
 - 9. Prostatic
 - 10. Of ovary
 - 11. Of testis

B. Internally Secreting

- 1. Pituitary
 - a. Of anterior lobe
 - b. Of posterior lobe
- 2. Thyroid
- 3. Parathyroid
- 4. Of islets of Langerhans of pancreas
- 5. Of suprarenal cortex
- 6. Of chromaffin tissue
 - a. Of suprarenal medulla
 - b. Of accessory bodies
- 7. Testicular
- 8. Ovarian
 - a. Of corpus luteum
 - b. Of Graafian follicle
- 9. Placental
- 10. Hepatic
- 11. Thymus
- 12. Pineal

IV. INTEGUMENT CELLS (Coverings and Linings)

A. Epithelial of skin and mucous membranes

- 1. Of skin
- 2. Of hair
- 3. Of nails

4. Of teeth (enamel organ)
6. Mucous membranes
 - a. Ciliated
 - b. Non-ciliated

B. Mesothelial

1. Peritoneal
2. Pericardial
3. Pleural
4. Of tunica vaginalis testis

C. Endothelial

1. Blood vascular
 - a. Arterial
 - b. Venous
 - c. Capillary
2. Lymphatic vascular
3. Endocardial

D. Other Linings and Coverings

1. Dura mater
2. Pia mater
3. Synovial cavities and bursae
4. Of membranous labyrinth
5. Of anterior and posterior chambers of eye
6. Of renal glomerulus
7. Of renal tubules (for reabsorption)

V. CELLS OF SUPPORTING TISSUE

A. Of Connective Tissue

1. Collagenous
2. Elastic
3. Reticular
4. Adipose
5. Mucous (vitreous humor)

B. Of Bone

C. Of Cartilage

VI. REPRODUCTIVE CELLS

A. Male

1. Spermatogonia
2. Spermatocytes I and II
3. Spermatids
4. Spermatozoa

B. Female

1. Primitive ova
2. Oögonia
3. Oöcytes
4. Mature ova

VII. HEMATOPOIETIC CELLS

A. Erythroblastic

1. Of bone marrow

B. Myeloblastic

1. Of bone marrow

C. Monoblastic

1. Of bone marrow
2. Of spleen

D. Lymphoblastic

1. Of bone marrow
2. Of spleen
3. Of lymph nodes
4. Of lymph nodules

E. Of Clasmatocyte Formation

1. Of bone marrow
2. Of spleen
3. Of lymph nodes
4. Of liver
5. Of connective tissue

F. Of Platelet Formation

1. Of bone marrow

VIII. FREE CELLS

A. Erythrocytes

1. Mature
2. Immature

B. Granulocytes

1. Mature
 - a. Neutrophiles
 - b. Basophiles
 - c. Eosinophiles
2. Immature
 - a. Myeloblasts
 - b. Myelocytes

C. Lymphocytes

1. Mature
2. Immature

*D. Monocytes**E. Clasmatocytes**F. Plasma Cells*

IX. EXTRACELLULAR SUBSTANCES

A. Solutions

1. Plasma
2. Lymph
3. Intercellular fluids
4. Fluids of serous cavities
 - a. Pleural
 - b. Pericardial
 - c. Peritoneal
 - d. Of tunica vaginalis testis
5. Aqueous humor
6. Endolymph and perilymph (of the internal ear)
7. Cerebrospinal fluid
8. Synovial fluid

B. Deposits

1. Matrix of bone
2. Enamel
3. Dentine
4. Matrix of cartilage
5. Connective tissue fibers
 - a. Elastic
 - b. Collagenous
 - c. Reticular

COMMON PARASITES OF MAN

I. ANIMALS PARASITES OF MAN

A. Protozoa

1. Rhizopoda (Ameboid protozoa)
 - a. *Endameba histolytica*
 - b. *Endameba coli*
 - c. *Endameba gingivalis*
2. Mastigophora (Flagellates)
 - a. *Leishmania donovani*
 - b. *Leishmania tropica*
 - c. *Trypanosoma cruzi*
 - d. *Trypanosoma gambiense*
 - e. *Trypanosoma rhodesiense*
 - f. *Trichomonas hominis*
 - g. *Trichomonas vaginalis*
 - h. *Trichomonas gingivalis*
 - i. *Giardia intestinalis*
3. Sarcosporidia
4. Sporozoa

<ol style="list-style-type: none"> a. <i>Plasmodium vivax</i> b. <i>Plasmodium malariae</i> c. <i>Plasmodium falciparum</i> d. <i>Plasmodium ovale</i> 	}	Malaria organisms
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5. Ciliata (Ciliates)
 - a. *Balantidium coli*

B. Spirochete

1. *Treponema*
 - a. *Treponema recurrentis*
 - b. *Treponema pallidum*
 - c. *Treponema vincenti*
 - d. *Treponema pertenue*
2. *Leptospira icterohemorrhagiae*

C. Platyhelminthes (Flatworms)

1. Trematoda (Flukes)

<ol style="list-style-type: none"> a. <i>Schistosoma hematobium</i> b. <i>Schistosoma japonicum</i> c. <i>Schistosoma mansoni</i> 	}	Blood flukes
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2. *Cestoda* (Tapeworms)
 - a. *Diphyllobothrium latum*
 - b. *Hymenolepsis*
 - (1) *Nana*
 - (2) *Diminuta*
 - c. *Taenia*
 - (1) *Saginata*
 - (2) *Solium*
 - d. *Echinococcus granulosus* (Hydatid disease)

D. Nematelminthes (Roundworms)

1. Nematoda
 - a. *Trichuris trichiura* (Whipworm)
 - b. *Trichinella spiralis* (Trichina worm)
 - c. *Strongyloides stercoralis*
 - d. *Ancylostoma duodenale*
 - e. *Ancylostoma braziliense*
 - f. *Necator americanus*

}	Hookworms
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- g. *Enterobius vermicularis* (Human oxyurid)
- h. *Ascaris lumbricoides*
- i. *Wuchereria bancrofti* (*Filaria bancrofti*)
- j. *Onchocerca volvulus* or *O. caecutiens* (Nodule filaria)
- k. *Loa loa* (Eye worm)
- l. *Dracunculus medinensis* (Guinea worm)

E. Arthropoda

- 1. Hexapoda (Insects)
 - a. *Calliphoridae* larvae (Blowfly)
 - b. *Pediculus humanus* (Body and head louse)
 - c. *Phthirus pubis* (Pubic louse)
- 2. Arachnida (Ticks, mites)
 - a. *Dermacentor venustus* (Tick)
 - b. *Sarcoptes scabiei* (Scab mite)
 - c. *Demodex folliculorum* (Hair follicle mite)
 - d. *Trombididae* (Harvest mite)

II. PLANT PARASITES OF MAN

Thallophytes

1. Bacteria

a. Cocci

- (1) *Staphylococcus pyogenes*
- (2) *Staphylococcus epidermidis*
- (3) Hemolytic streptococci
- (4) Non-hemolytic streptococci
- (5) *Pneumococcus*
- (6) *Gonococcus*
- (7) *Meningococcus*

b. Bacilli

- (1) *Bacillus influenzae*
- (2) *Bacillus Koch-Weeks*
- (3) *Bacillus pertussis*
- (4) *Bacillus ducrey*
- (5) *Bacillus typhosus*
- (6) *Bacillus paratyphosus-A*
- (7) *Bacillus paratyphosus-B*
- (8) *Bacillus enteritidis*
- (9) *Bacillus aertrycke*
- (10) *Bacillus suispestifer*
- (11) *Bacillus dysenteriae*
- (12) *Bacillus coli communis*
- (13) *Vibrio cholerae*
- (14) *Bacillus mallei*
- (15) *Corynebacterium diphtheriae*
- (16) *Bacillus tuberculosis*
- (17) *Bacillus leprae*
- (18) *Brucella melitensis*
- (19) *Bacillus anthracis*
- (20) *Bacillus pestis*
- (21) *Bacillus tetani*
- (22) *Bacillus botulinus*
- (23) *Bacillus welchii*
- (24) *Bacillus tularensis*
- (25) *Bacillus of granuloma inguinale*

2. Fungi

a. *Phycomycetes*

- (1) *Coccidioides*
- (2) *Mucor*

b. *Ascomycetes*

- (1) *Saccharomyces*
- (2) *Cryptococcus*
- (3) *Endomyces*
- (4) *Monilia*

c. *Fungi imperfecti*

- (1) *Oidium*
- (2) *Torula*
- (3) *Madurella*
- (4) *Glenospora*
- (5) *Sporotrichum*
- (6) *Trichosporium*
- (7) *Aspergillus*
- (8) *Penicillium*
- (9) *Scopulariopsis*
- (10) *Microsporon*
- (11) *Epidermophyton*
- (12) *Endodermophyton*
- (13) *Favus*
- (14) *Actinomyces*
- (15) *Leptothriceae*

3. Disease agents of unknown relationships

a. Filterable viruses of

- (1) Smallpox
- (2) Encephalomyelitis
- (3) Herpes zoster
- (4) Herpes simplex
- (5) Varicella
- (6) Epidemic encephalitis
- (7) Poliomyelitis
- (8) Rabies
- (9) Trachoma
- (10) Molluscum contagiosum
- (11) Warts
- (12) Mumps
- (13) Measles
- (14) Dengue
- (15) Pappataci

4. *Rickettsia*

- a. *Rickettsia prowazeki* (Typhus)
- b. *Dermacentroxenus rickettsii* (Rocky Mountain spotted fever)
- c. *Rickettsia quintana* (Trench fever)
- d. Tsutsugamushi disease

Such an outline gives us an oversight of the body, the types of tissue of which it is made, and some of the organisms with which it is at times infested. It is the type of arrangement which might be used in a course or book but not in a systematic index which would be arranged alphabetically.

I wish to thank those in our department who have so kindly put up with my attempts at reorganization, and also Dr. Sam L. Clark and Dr. Ernest W. Goodpasture for their very helpful advice and suggestions, as well as Dr. Herbert S. Wells, who spent much time on this when with us.

INDEXING

At present we have no systematic method or place for recording the reaction of the organism to drugs. It is obvious that at some time this will become necessary and some system must be started, either in connection with some current index or as a separate (and costly) venture. Already certain tissues are known to be affected by hundreds of chemical substances as, for example, the various hypnotics and anesthetics, among which almost one thousand barbiturates alone have been made. In order to give an idea of how such a plan might be carried out, consider one type of tissue, muscle.

Tissue Types. Under any one tissue, as muscle, we find varieties, as cardiac, smooth, skeletal, and uterine. Under these main types, we may discover further subdivisions as shown in the case of smooth muscle. Just how such types of tissue will be named in the future is but one of our problems, but an important one.

SMOOTH MUSCLE

A. Contracts with epinephrine.	Relaxes with acetylcholine.
B. Relaxes with epinephrine.	Contracts with acetylcholine.
C. Contracts with epinephrine.	No response with acetylcholine.
D. No response with epinephrine.	Contracts with acetylcholine.
E. Contracts with epinephrine.	Contracts with acetylcholine.

Tissue Properties and Functions. Under any one type of tissue we may list alphabetically its properties, functions, or other information which we wish, as indicated.

Reaction to Chemical Substances. Having discovered the specific response of a function of one type of tissue, the reference to the work proving this may be recorded by placing the name of the substance under the proper tissue function and giving the reference after this.

Animal Used. Recording the type of animal used in each entry obviates a whole separate classification for each species. Tissues not occurring in man, as the nictitating membrane of the cat, can be added to the list of tissues, giving the name of the species after it.

Method. One of the most pressing needs of the pharmacologist today is what might be called a pharmacological analysis. What pharmacologist has at his fingertips the methods necessary to study the reaction of the tissues here outlined to any new drug? By recording with each entry the method used, one would automatically have such an outline. If the drug were of interest, as producing local anesthesia, one could look under nerve, sensory neurones of pain, and find a list of drugs already used and references to the methods by which these results were obtained.

Chemistry. In rare instances we know that certain chemical substances within the cell react with drugs to which the cells are exposed; for example, oxyhemoglobin reacts with carbon monoxide, the oxygen being replaced by the latter. In the same way, glutathione reacts with arsenic. In such cases we may record these reactions under "Chemistry," giving first the substance contained in the cell and, under this, the substance which reacts with it.

Pathological Conditions. Pathological tissue can be treated exactly as other tissue, and it would seem unnecessary to set aside a separate section for such discussion. In the case of recording the effect of digitalis in congestive heart failure on the contractility of pathological heart muscle, we would look under cardiac muscle, pathological conditions, then under that function in which we are interested—contractility, and under this place the substance, digitalis, followed by the response produced, together with a reference.

MUSCLE

Cardiac

Chemistry

Metabolism depressed by

Arsenic: reacts with glutathione. Voegtlin, Dyer and Leonard: U. S. Public Health Reports, 1923, xxxiii, 1882.

Distribution

Heart only

Functions

Conductivity decreased by

Ephedrine: (dog and rabbit) electrocardiographic studies. Chen and Meek: Jr. Pharmacol. and Exper. Therap., 1926, xxviii, 31.

Contractility increased by

Digitalis: (dog) optical recording of intraventricular pressure. Wiggers and Stimson: Jr. Pharmacol. and Exper. Therap., 1926, xxx, 263.

Irritability decreased by

Acetyl- β -methylcholine: (man). Starr: Am. Jr. Med. Sci., 1933, clxxxvi, 330.

Refractivity increased by

Quinidine: (turtle) muscle strips. Wedd: Am. Jr. Physiol., 1934, cviii, 265.

Rhythmicity

Rate increased by

Caffeine: (rabbit) perfused heart. Heathcote: Jr. Pharmacol. and Exper. Therap., 1921, xvi, 327.

Innervation

Sympathetic: cardiac branches of the stellate ganglia, few fibers directly from second to fourth thoracic ganglia.

Parasympathetic: cardiac branches from the vagi.

a. Fibers from right vagus mainly to the sinus node.

b. Fibers from the left vagus to the auricular ventricular node.

Internal conducting system: Purkinje fibers and nodal tissue. The left auricle is apparently without this system.

Structure

Cells are large, cross-striated; arise from a syncytium but in the adult there are intracellular discs; are branched and fibrils run from one to another. Nuclei are centrally located.

*Pathological Conditions**Contractility*

Congestive heart failure

Digitalis: (man) returned to normal as shown by x-ray. Stewart et al.: Arch Int. Med., 1938, lxii, 569.

Irritability

Chloroform

Epinephrine: (dog) increased to fibrillation. Levy: Heart, 1913, iv, 319.

Secondary Reactions. Obviously, it is not enough to know about the reaction of the organism to epinephrine, that vascular smooth muscle contracts after its injection. One wants to know what actually happens to the blood pressure, heart rate, blood volume, and to the animal as a whole. *This can never be known except by a systematic study of the reaction of the individual parts of the organism and the resultant secondary reactions.* There will be countless secondary reactions which may or may not have been analyzed which are, however, facts and can be recorded as, for example, blood pressure and respiration rate which are affected by practically every known substance. It is self-evident that if one wants the entire picture of the organism's reaction this will be found under the name of the substance producing the reaction which will necessitate a chemical index arranged according to one of the accepted chemical methods. Here one can record everything about the drug as is done in books on lead and on sulfanilamide.

DISCUSSION AND CONCLUSIONS

We have seen that the original pharmacists, medicine men, or magicians discovered the magic of life in chemical molecules, that as everything is made of these molecules, we are all studying chemistry in one form or another. There are, however, two main groups of "chemists," those studying the science of chemistry, the structure and properties of the chemical substances, and those studying special chemical agglomerations, that is, living plants and animals, or inanimate structures.

The medical group has existed for thousands of years as a special entity. They are not general biologists or chemists but have one purpose only, that is, to study the human organism in health and disease. The pharmacists, on the other hand, split off from this group early, as shown in figure 1, and studied drugs and later chemical substances. The interests of the pharmacist or chemist are not those of the medical man. He does not belong in the medical group; he has never been at home there as the pharmacist or as a teacher of *materia medica*.

Pharmacology has been shown to differ in no way from pharmacy. It arose from Buchheim's misconception that we can have a medical group

studying the "action of drugs." One must choose and study the drugs or the human organism, but one cannot make a science of the vacuum between the two. That our interest lies in the human organism and not in drugs has been demonstrated by the writings of practically all of Buchheim's followers. In spite of the general realization of this, pharmacology is still considered and taught as a study of drugs and their actions. One reason for this is the lack of any systematic method of studying the reaction of the body to drugs. Without system we have no science, and pharmacology today is not a science but merely a practical study of certain substances without system or order.

By considering the organism as a community of cells which can be arranged in classes regardless of location in the organism, we have suggested a systematic method of studying the reaction of the organism to chemical substances, as well as a method for recording our data in a systematic manner.

If that medical group known as pharmacologists would give up the study of drugs and study the body by means of its reaction to chemical substances, using these as his tools, he would be able to develop a systematic medical science and, in so doing, *would give us the information necessary for the building of a sound basis for rational therapeutics.*

Whether one starts with a *single drug* and studies the reaction of the organism to it, or with the organism and studies its reaction to a *single* chemical substance, makes no difference; but the end result of studying hundreds of thousands of chemical substances and their "actions," present-day pharmacology, and studying the human organism systematically by means of its reaction to chemical substances will be found to be very different things and to have far-reaching consequences. Ten years' experience with the latter method has convinced me of this.

Everyone will use this method of studying the body by means of its reaction to chemical substances. This is as it should be, but it is the function of our group only, to systematize this knowledge, to arrange the tools for use by others, and to be the custodian of that immensely important group of facts, namely, the means by which we can initiate, depress, or change specific functions of the organism.

The industrial chemist, pharmacist and/or pharmacologist will be of ever-increasing aid to the medical group. They will not only make new chemical substances, but they will want to know the reaction of the organism to *their particular product*. This will necessitate investigation, the need of trained men, and the very pressing need of the proper recording of our data. Where would the chemists be financially if they had no way of knowing what substances have already been made? We have at present only the crudest possible methods of finding those substances to which a given tissue reacts.

From this discussion it is suggested that the medical profession realize that the study of drugs, their actions, pharmacy, or its analogue phar-

macology, is not a true medical science; that we complete the long evolution of pharmacy by divorcing it as well as pharmacology from medicine and developing a new medical science differentiated from the other branches of medicine by the tools and methods which it uses, namely, the study of the human organism by means of its reaction to chemical substances.

Space will not allow a consideration of how such a plan of studying the body should be taught. The relationship of materia medica, pharmacy, pharmacology, prescription writing, dosage, toxicology, chemotherapy, and therapeutics has been discussed at length in the numerous articles referred to above, and it is the author's intention to outline in more detail the actual application of such a plan in a future communication.

Names may do good or evil. The name "Pharmacology" has certainly led us astray for nearly one hundred years. Any name which would divorce such a group as described above from pharmacy and describe a truly medical science would answer our purpose. "Biotrepy" or "Biotrepology" is suggested, from *bios*, life, and *trepo*, to change, or even "Chemobiotrepy."

After the revolutionary discoveries of the sulfonamides, great interest will be shown in studying "drugs" and great sums of money expended in such investigations; but the discovery of ether, as well as that of Salvarsan, although by no means insignificant, failed to put pharmacology on a sound basis. After thousands of years of experimentation, when it has been finally demonstrated beyond doubt that we cannot only relieve, but cure disease by the use of drugs, it would seem time to consider seriously the matter of the proper organization of this most important branch of medicine.*

BIBLIOGRAPHY

1. CUTTER, W. D.: Influences and trends in medical education in the United States, Inauguration and Symposium at Vanderbilt University, 1938, 117.
2. GRIESINGER, W.: Zur Revision der heutigen Arzneimittellehre, Arch. f. physiol. Heilk., 1847, vi, 381, 507; 1848, vii, 1.
3. KÜCHENMEISTER: Einige kritische Bemerkungen zur Arzneimittellehre, Wien. med. Wchenschr., 1851, i, 589, 605.
4. FRASER, T. R.: Inaugural address by the president of the section of materia medica and pharmacology, Trans. Internat. Med. Cong., 7th sess., London, 1881, i, 441.
5. BEYER, H. G.: On some of the problems to be solved by pharmaco-physiology, with a new outline classification of pharmacology, Med. News, Philadelphia, 1887, li, 169.
6. FRASER, T. R.: The position of materia medica in the curriculum of study, Brit. Med. Jr., 1892, ii, 1157.

* Since this paper was read, the following statement appeared in "The Rockefeller Foundation, A Review for 1938" by Raymond B. Fosdick: "Though no subject in medicine would seem more important than pharmacology, which deals with the action of drugs and their use in disease, this field of medicine is hampered by lack of adequate financial support. In twenty-five recognized American medical schools there are no separate departments of pharmacology, the subject being combined for economic reasons with physiology or biochemistry. In many other schools where there is a separate division, the subject receives but meager support. This situation is doubtless responsible for the failure of pharmacology to attract recruits and for the shortage of outstanding younger men to fill professional chairs which are becoming vacant. Larger support is needed not only to promote fruitful research in this important field but also to improve the teaching on the applied side—the administration of drugs—which is notably weak in most American medical schools."

7. JEROME, W. J. S.: A public lecture on pharmacology: its aims and methods, *Lancet*, 1898, i, 1599.
8. STOCKMAN, R.: The teaching of materia medica, *Edinburgh Med. Jr.*, 1898, iii, 32.
9. BRADBURY, J. B.: The place of pharmacology in medical curriculum, *Brit. Med. Jr.*, 1899, ii, 402.
10. ABEL, J. J.: On the teaching of pharmacology, materia medica and therapeutics in our medical schools, *Philadelphia Med. Jr.*, 1900, vi, 384.
11. CLOETTA, M.: Über den Unterricht in der Arzneimittellehre, *München. med. Wchnschr.*, 1902, xlix, 25.
12. HILL, W. B.: The place and importance in college curriculum of materia medica, *Jr. Am. Med. Assoc.*, 1902, xxxix, 546.
13. SOLLMANN, T.: Teaching of therapeutics and pharmacology from the experimental standpoint, *Jr. Am. Med. Assoc.*, 1902, xxxix, 539.
14. SOLLMANN, T.: The teaching of materia medica in medical schools, *Jr. Am. Med. Assoc.*, 1904, xliii, 452.
15. BERGELL, P.: Über die moderne Gestaltung des pharmakologischen Unterrichts, *Deutsche med. Wchnschr.*, 1908, xxxiv, 882.
16. DICKEY, W. A.: The necessity of added emphasis in the teaching of therapeutics and pharmacology, *Lancet-Clinic, Cincinnati*, 1908, c, 88.
17. MACNIDER, W. DEB.: The teaching of pharmacology in the smaller medical schools, *South. Med. Jr.*, 1909, ii, 904.
18. SOLLMANN, T.: The current problems of pharmacology and therapeutics, *Jr. Am. Med. Assoc.*, 1912, lix, 833.
19. BLUMER, G.: The need of reorganization in the methods and teaching of therapeutics, *Boston Med. and Surg. Jr.*, 1913, clxix, 261.
20. CRAWFORD, A. C.: Conclusions from an experiment in teaching pharmacology, *Boston Med. and Surg. Jr.*, 1913, clxix, 274.
21. CUSHNY, A. R.: Progress in materia medica, *Edinburgh Med. Jr.*, 1918, xxi, 317.
22. FRASER, T. R.: Teaching of therapeutics and materia medica, *Edinburgh Med. Jr.*, 1918, xx, 380.
23. HIRSCHFELDER, A. D.: Teaching of pharmacology, *Jr. Am. Med. Assoc.*, 1918, lxxi, 609.
24. MARSHALL, C. R.: Teaching of therapeutics and materia medica, *Edinburgh Med. Jr.*, 1918, xx, 384.
25. SILLAR, W. C.: Teaching of materia medica, *Edinburgh Med. Jr.*, 1918, xx, 386.
26. STOCKMAN, R.: Teaching of materia medica, *Edinburgh Med. Jr.*, 1918, xx, 389.
27. EDMUNDS, C. W.: The teaching of pharmacology, *Proc. Assoc. Am. Med. Coll.*, 1920, xxx, 128.
28. DIXON, W. E.: Place of pharmacology in medical curriculum, *Brit. Med. Jr.*, 1922, ii, 410.
29. READ, B. E.: New viewpoint of pharmacology, *China Med. Jr.*, 1922, xxxv, 567.
30. BIERRING, W. L.: The teaching of pharmacology, *Proc. Assoc. Am. Med. Coll.*, 1924, xxxiv, 46.
31. HANDOVSKY, H.: Place of general pharmacology in natural science, *Deutsch. med. Wchnschr.*, 1924, i, 1315.
32. MEYER, H. H.: Fifty years of experimental pharmacology, *Deutsch. med. Wchnschr.*, 1924, i, 1701.
33. JARISCH, A.: Aims of pharmacology, *Klin. Wchnschr.*, 1925, iv, 76.
34. CLARK, A. J.: Relation between pharmacology and clinical medicine, *Edinburgh Med. Jr.*, 1927, xxxiv, 185.
35. TIFFENEAU, P.: Teaching of pharmacology, *Paris méd.*, 1927, lxiii, 197.
36. WATT, J. M.: Nature of pharmacology and therapeutics with observations on their teaching, *Jr. Med. Assoc. S. Africa*, 1927, i, 200.
37. BONAR, M. L.: Teaching of pharmacology, *Jr. Assoc. Am. Med. Coll.*, 1929, iv, 313.

38. EDMUNDS, C. W.: Pharmacology and the medical schools, Jr. Am. Med. Assoc., 1930, xcv, 383.
39. EICHHOLTZ, F.: History and problems of pharmacology in East Prussia, Deutsche med. Wchnschr., 1930, lvi, 1526.
40. STARKENSTEIN, E.: History: Development and teaching of pharmacology in Prag, Med. Klin., 1929, xxv, 1720.
41. TIFFENEAU, P.: Teaching, pharmacologic instruction and research laboratory of Paris School of Medicine, Paris méd., 1930, lxxvi, 602.
42. ZUNZ, E.: Teaching, pharmacologic instruction and research laboratories of Faculte de Medicine at Bruxelles, Paris méd., 1931, lxxx, 593.
43. MACNIDER, W. DEB.: Teaching of pharmacology, South. Med. Jr., 1932, xxv, 309.
44. TIFFENEAU, M.: Evolution of teaching of pharmacology and research on pharmacodynamics in Great Britain and Belgium, Paris méd., 1932, lxxxvi, 48.
45. WALDEN, P.: History, a century of discoveries and findings, Med. Klin., 1934, xxx, 493.
46. KOPPANYI, T.: Teaching of pharmacology, Jr. Assoc. Am. Med. Coll., 1935, x, 338.
47. SEEL, H.: Die Aufgaben der klinischen Pharmakologie, Deutsche med. Wchnschr., 1935, lxi, 1968.
48. DAVID, N. A., and EMERSON, G. A.: The present status of research and teaching in pharmacology, Jr. Am. Med. Assoc., 1936, cvii, 1599.
49. DEGRAFF, A. C.: Teaching of therapeutics, Jr. Assoc. Am. Med. Coll., 1936, xi, 65.
50. EDMUNDS, C. W.: The teaching of pharmacology, Jr. Assoc. Am. Med. Coll., 1936, xi, 83.
51. HAYMAN, J. M., JR.: The teaching of pharmacology from the standpoint of the clinician, Jr. Assoc. Am. Med. Coll., 1936, xi, 77.
52. HEUBNER, H.: Zum Begriff der "Klinischen Pharmakologie," Deutsch. med. Wchnschr., 1936, lxii, 558.
53. MACNIDER, W. DEB.: The teaching of pharmacology from the standpoint of the examiner, Jr. Assoc. Am. Med. Coll., 1936, xi, 70.
54. SEEL, H.: Zum Begriff der "Klinischen Pharmakologie," Schlusswort hierzu, Deutsch. med. Wchnschr., 1936, lxii, 560.
55. MEYER, H. H.: Experimental pharmacology and practical therapeutics, Cong. internat. de l'Union therap., 1937, i, 24.
56. LAMSON, P. D.: A possible remedy for the present depression in pharmacology, Jr. Am. Med. Assoc., 1931, xcvi, 1312.
57. SCHMIEDEBERG, O.: Rudolf Buchheim, sein Leben und seine Bedeutung für die Begründung der wissenschaftlichen Arzneimittellehre und Pharmakologie, Arch. f. exper. Path. u. Pharmakol., 1911, lxvii, 1.
58. BUCHHEIM, R.: Lehrbuch der Arzneimittellehre, 3rd Ed., 1878, Voss, Leipzig.
59. DYSON: The chemistry of chemotherapy, 1928, Ernest Benn, Ltd., p. 268.
60. MEYER, H. H.: Schmiedeberg's Werk, Arch. f. exper. Path. u. Pharmakol., 1922, xcii, VII.
61. BRUNTON, T. L.: A text-book of pharmacology, therapeutics and materia medica, 3rd Ed., 1889, adapted to the U. S. Pharmacopoeia by F. H. Williams, Lea Brothers and Co., Philadelphia.
62. MEYER and GOTTLIEB: Die experimentelle Pharmakologie als Grundlage der Arzneibehandlung, 1st Ed., 1910, Urban & Schwarzenberg, Berlin.
63. SOLLMANN, T.: A manual of pharmacology and its applications to therapeutics and toxicology, 1st Ed., 1917, W. B. Saunders, Philadelphia.
64. LAMSON, P. D.: The future of pharmacology. Presented at the Peter Bent Brigham Hospital Reunion, Boston, May 1938.
65. HERTWIG: Lehrbuch der Zoologie, 10th Ed., 1912, Fischer, Jena. (Translated by Kingsley.)

CASE REPORTS

HICCUP AS A COMPLICATION OF ACUTE CORONARY ARTERY OCCLUSION *

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HICCUP as a complication of an acute coronary artery occlusion is not mentioned in the literature. In the past year I have encountered this annoying and distressing symptom in three cases. In one patient the hiccups commenced about four hours after the onset of the painful features of the occlusion and lasted with varying severity for five days. In the other two cases they appeared on the second day following the occlusion and lasted, also with varying intensity, two and four days respectively. In one patient they ceased suddenly and in the others gradually subsided. Two of the patients had an uneventful recovery from the cardiac infarction. The other died with recurrent attacks of pulmonary edema two days after the hiccups had ceased. While the hiccups were extremely weakening and interfered with proper rest, it is difficult to consider their presence a contributing cause of the death of this patient because, aside from having had hypertension and angina pectoris for many years, he had had a previous coronary occlusion six months before the fatal attack.

Treatment was of no avail in abolishing the hiccups. All the usual remedies gave only temporary relief. Sedatives and opiates were of value in lessening the force of the diaphragmatic spasms and alleviating the resultant soreness of the chest and abdominal muscles. The results from the inhalation of 5 per cent carbon dioxide in oxygen were variable and not constant. In one patient who obtained relief on three separate occasions from its use, the carbon dioxide the fourth time caused cessation of audible cardiac activity for approximately two minutes. In view of the harmful results in individuals with heart disease from induced oxygen want,^{1,2} carbon dioxide should be cautiously administered and then only in low concentration.

The cause for the hiccups in these patients is obscure. Constitutional diseases such as diabetes or uremia were not present. All intra-abdominal factors were eliminated. Particular attention was paid to proper intestinal and urinary bladder evacuation. Local pressure was not a factor. There was no evidence that they originated from disease of the central nervous system. It is possible that an infarction of that portion of the ventricle resting on the diaphragm with resultant diaphragmatic irritation was responsible. A localized pericarditis with irritation of the phrenic nerve is also to be considered. Hiccup accompanying pericarditis has been mentioned in the literature.

SUMMARY

Three cases of acute coronary occlusion complicated by hiccups have been encountered in the past year. The cause is obscure. They have no apparent prognostic significance. Treatment is disappointing.

* Received for publication May 12, 1938.

REFERENCES

1. KATZ, L. N., HAMBURGER, W. W., and SCHUTZ, W. J.: Effects of generalized anoxemia on the electrocardiogram of normal subjects. Its bearing on the mechanism of attacks of angina pectoris, *Am. Heart Jr.*, 1934, ix, 771-781.
2. LEVY, R. L., BARACH, A. L., and BRUENN, H. G.: Effects of induced oxygen want in patients with cardiac pain, *Am. Heart Jr.*, 1938, xv, 187-200.

PRIMARY JEJUNAL ULCER; REPORT OF A CASE WITH RUPTURE AND RECOVERY *

By F. EUGENE ZEMP, M.D., F.A.C.P., *Columbia, S. C.*

PRIMARY jejunal ulcer is a very rare condition and differs in its clinical manifestations considerably from ulcers involving other parts of the gastrointestinal tract. Richardson¹ collected 12 cases in 1922. In 1933 Ebeling² made a survey of both domestic and foreign literature and presented a summary of the important findings in 47 collected cases and reported a case of his own. Since then Puhl,³ and Hall⁴ have each reported one case. Each case thoroughly studied, should add to its clinical entity.

CASE REPORT

E. B. R., a white male, 59 years of age, complained of pain in the lower abdomen. The family history was negative. He had had the usual childhood diseases, and typhoid fever at the age of 10. Twenty years ago he had experienced a severe case of diarrhea, which lasted three weeks and was undiagnosed as to etiology. There had been no operations or injuries. He drank four or five cups of coffee a day, occasionally tea, coca colas, and cocktails, and smoked rather heavily, consuming about 30 cigarettes a day. He slept well, but was of a nervous temperament and easily upset. He had lost 14 pounds during the past year.

The present illness had begun nine years ago, with pains in the lower abdomen, which were spasmodic in character and occurred at varying intervals. During the past five months they had been very severe and had caused him considerable discomfort. They were described as "a hurting" and "colicky-like," and occasionally there would be a gnawing or burning sensation in the epigastric region, not related to eating. Lying on his stomach gave some relief, and complete relief from a few days to a week or more occurred at various intervals. His appetite was good and there was no nausea or vomiting, but considerable gas with distention. Although constipated most of the time, he occasionally had a watery stool. Immediately after a bowel movement, his abdomen often became distended, especially if a laxative had been taken.

On physical examination he was 6 ft. 1½ inches tall, weighed 142 pounds, and was somewhat pale. His scalp, ears, and nose were negative. The pupils were normal in size and shape, and reacted promptly to light. There was no exophthalmos or icterus. The eye grounds were negative. His teeth were false. The examination of the throat was negative. There were no enlarged glands in the neck, but in the isthmus of the thyroid gland was a small hard nodule about the size of a marble. The chest was well developed; expansion was good, and the lungs were clear. There was no enlargement of the heart, and its action was normal. The blood pressure was

* Received for publication May 10, 1938.

132 mm. of mercury systolic and 70 diastolic. The abdomen was slightly scaphoid in shape, soft and relaxed, and no masses were palpable. The abdominal aorta was palpable, and descending colon contracted. The liver edge could not be felt, and there was no tenderness over the gall-bladder area. The spleen was not palpable, and nothing abnormal was felt in the kidney regions. The extremities were normal in size and shape. All reflexes were active and normal. The brachial arteries felt somewhat thickened. The genitalia were normal, except for a slightly enlarged epididymis. The prostate gland was firm, and the left lobe was slightly larger than the right. Proctoscopic examination revealed a normal mucous membrane.

In the laboratory studies the red blood cells were 3,890,000, hemoglobin 78 per cent, white blood cells 7,400 with 69 per cent polymorphonuclear leukocytes. The Wassermann and Kahn tests were negative. The urine had a specific gravity of 1.012, dark amber, acid, and did not contain any albumin or sugar. The microscopic study was normal. In the fractional gastric analysis the free hydrochloric acid ranged from 40 degrees to 70 degrees, and the total acids from 60 degrees to 78 degrees. On May 1, 1937, the examination was completed with a fluoroscopic study of the chest, stomach, and duodenum. The findings were normal, except for a moderate ptosis. A roentgen examination of the genito-urinary tract was also normal.

My impression, after the examination, was that there was a moderate viscer-optosis with gastric hyperacidity, and probably an ulcer, very small or not demonstrable. He was, therefore, placed on an ulcer diet with the usual alkalies. Slight improvement followed for two weeks, at which time visible peristaltic waves were noted in the mid-abdomen. Because of this, a barium enema was given which was negative. He continued treatment, but did not improve. On May 20, 1937, the visible peristaltic waves were more prominent, and he complained of colicky-like pains in the lower abdomen with distention. An exploratory operation was advised, as a tumor of the small intestine was suspected, due to the mild obstructive symptoms. One week later, on May 6, 1937, he was taken suddenly ill with severe pains throughout the abdomen. Examination revealed a board-like rigidity with tenderness throughout. He was sent immediately to the Columbia Hospital. His temperature was 101° F., pulse 125, and blood pressure 110 systolic and 62 diastolic. The white blood cells were 7,500 with 84 polymorphonuclear leukocytes. A preoperative diagnosis of perforated duodenal ulcer was made; and that afternoon he was operated on by Dr. George Bunch. There was a segment of the upper jejunum that was red and congested with the omentum partially adherent on one side, and at this point an acute perforation was found of an antimesenteric ulcer about eight inches below the ligament of Treitz. The peritoneal cavity and the pelvis contained a ropy mucoid exudate. The ulcer was infolded with interrupted linen sutures, and a tag of freed omentum unattached was sutured over the closure. A large drain was inserted and the wound closed.

During the postoperative period the distention was relieved by a Levine tube for five days, and he was given glucose intravenously and by hypodermoclysis daily. At the end of six days he was placed on an ulcer regime, and left the hospital on July 10. He continued to improve and has not had any symptoms of importance up to the present time. On August 1, 1938, the jejunum was thoroughly studied by fluoroscopic and roentgen-ray examination, and there was no evidence of the ulcer or of any abnormal findings.

In conclusion, I wish to suggest as an aid to diagnosis, the more use of the five hour barium meal fluoroscopically in the non-perforated cases and the roentgenogram in the erect position in the perforated cases. The former frequently shows a dilatation of the jejunum proximal to the lesion with regurgitation of the barium and the latter an air bubble under the diaphragm.

BIBLIOGRAPHY

1. RICHARDSON, E. P.: Jejunal ulcer without previous gastroenterostomy, *Surg., Gynec. and Obst.*, 1922, xxxv, 1.
2. EBELING, W.: Primary jejunal ulcer, *Ann. Surg.*, 1933, xcvii, 857.
3. PUHL, H.: Primary jejunal ulcer with heterotopic mucosa of the fundus, *Deutsch. Ztschr. f. Chir.*, 1933, ccxxxix, 624.
4. HALL, D. P.: Perforation of a primary jejunal ulcer, *South. Surg.*, 1936, v, 309.

MINOR INJURIES OF THE CERVICAL SEGMENT OF THE SPINE AND THEIR CONSEQUENCES

Case Report *

By ALFRED GORDON, F.A.C.P., *Philadelphia, Pennsylvania*

THE majority of recorded cases of injuries of the cervical spine are instances of gross damages, such as dislocations or fractures of the vertebrae with secondary gross lesions in the spinal cord, leading to muscular atrophies or spastic paralysis of the extremities as the result of tracts—degeneration, with involvement of the sphincter of the bladder and occasionally, in males, persistent priapism. Cases of less severe damage are not common and frequently are not recognized. The cord symptoms in such cases are at first very slight; the moderate initial disability is looked upon with no special concern and the prognosis is ordinarily considered very favorable for a complete recovery. Nevertheless close and prolonged observation will reveal that the apparently mild disturbances have for an underlying basis serious lesions in the cord itself. As an example of such apparently minor lesions demanding recognition and serious consideration, the following case is reported.

CASE REPORT

P. M., aged 50, a laborer, was driving a truck in October 1936, when the horse became frightened, ran off at a high speed and hit a pole. The driver was thrown off; the vertex of his head struck the ground, producing excessive anterior flexion of the cervical spine. There was no loss of consciousness, the patient was merely "dazed." During the following two weeks there was gradual development of pain in the neck and weakness in both arms. The patient was admitted to Coatesville Hospital where the head was immobilized and kept in an apparatus during eight weeks. After the removal of the latter, the patient was unable to move his head in any direction, could not raise his left arm above the shoulder and was troubled by muscular twitchings in both arms.

Upon examination at that time, the following condition was found: Roentgenological examination of the cervical vertebrae showed no fracture and no dislocation, but the intervertebral space between the sixth and seventh vertebrae was a little wider on the right than on the left side. The neck was rigid and no flexion, extension, rotation, or lateral movements could be obtained without causing considerable pain. The left arm could be raised only partially, although the shoulder-joint presented no evidence of damage (the roentgen-ray of the joint was negative and the head of the humerus could be rotated in the cavity without difficulty). There was apparently no atrophy of the muscles of the arms and no reactions of degen-

* Received for publication April 4, 1938.

Patient presented at the April Meeting of the Philadelphia Neurological Society.

eration could be obtained. The grip of both hands was good. The biceps and triceps reflexes on both sides were at times greatly diminished, and usually were unobtainable. By percussing the lower end of the radius on the left side, a slight flexion of the fingers was sometimes induced. This is the so-called "inversion reflex of the radius," characteristic, according to Babinski (1910), of an injury of the fifth cervical segment of the spinal cord. The third striking symptom in this case was continuous muscle-waves (myokymia) and fibrillary contractions of the flexors and extensors of both upper arms, more on the left than on the right side. The myokymia would become more pronounced upon mechanical irritation of the same muscles. Moreover, at times simultaneously with the clonic manifestations there were also sudden tonic spasms of the muscles of the forearm, but only on attempts to carry out abrupt voluntary movements. Finally it was observed that the scapulo-humeral tendon reflex was more marked on the left than on the right side. Percussion of the middle of the inner border of the scapulae produced abduction and external rotation of the entire arm, more on the left than on the right side. All forms of sensation were normal in the upper extremities.

The tendon reflexes of the lower extremities were increased, but there were no pathological reflexes. The sphincters had never been affected since the accident. The pupils also had been normal. Blood and urine were normal in every respect. The Wassermann test was negative and the spinal fluid was normal.

The patient's further course showed complete restoration of the function of the cervical muscles and considerable improvement in raising the arms. The objective pathological symptoms at present are: difficulty of obtaining tendon reflexes in the upper extremities; the occasional presence of "inversion of the radial reflex"; and finally continuous muscle-waves and fibrillary contractions of the muscles of both upper arms.

COMMENT

The muscular phenomena observed here belong to the large group of myoclonias. Several clinical types have been described: (a) Para-myoclonus multiplex, in which there is a simultaneous involvement of many muscles of the body; (b) Unverricht's type of myoclonus, in which myoclonic contractions are intensified by physical exertion and emotional stimuli and are associated with epilepsy; (c) Lundborg's type, in which clonic and tonic muscular contractions take place during an emotion, an embarrassment, and upon the slightest sensory stimulation (psychoclonic, psychotonic and sensoclonic reactions respectively); (d) myotonoclonic type of Popoff, in which clonic phenomena, during voluntary movements, are followed after a long interval by tonic muscular contractions; (e) Lenoble-Aubineau's type (nystagmus-myoclonia) which is characterized by simultaneous spasmodic twitchings of the muscles of the extremities and of the eye-globes associated with tremor of the head and is a familial disease in which are also found physical stigmata of degeneration; (f) the myoclonic post-encephalitic sequelae with or without typical parkinsonism, the muscular contractions of which may affect any part of the body including the palate, pharynx, uvula and even the diaphragm; (g) "acute infectious myoclonus multiplex," described by Hunt, characterized not only by myoclonic twitchings, but also by general signs of an infectious nature, such as fever, headache, pain at each myoclonic paroxysm and delirium; (h) finally myoclonia which manifests itself in the form of muscle-wave (myokymia) and fibrillary contractions.

Irrespective of the variety, all forms of myoclonia are characterized by the common symptom of paroxysms of involuntary and irregular clonic contrac-

tions of groups of muscles. The case described above belongs to the last clinical type. The wave-like muscular phenomenon (myokymia) combined at times with fibrillation, especially upon mechanical stimulation, is limited here to the flexor and extensor group of muscles in the upper arms, more on the left than on the right side. Considering the association of this symptom with the history of trauma in the cervical region of the spine, one is gradually led to the question of the pathogenesis of the myokymia.

Various authors have expressed divergent views concerning the origin of myoclonic dyskinesias. The so-called muscular view, according to which the phenomenon is myopathic in origin, is not satisfactory, particularly in cases of the type recorded here. Wagner-Jauregg's theory of a causal disturbance in the function of the thyroid and parathyroid glands cannot be applied to all cases of myoclonia. The explanation of the phenomenon on an exclusively psychogenic basis (hysteria, etc.) is equally unsatisfactory in most instances; in fact, the majority of authors believe in an organic origin of all cases of myoclonic twitchings. Friedreich was the first to hold such a view. He considers the muscular phenomena due to irritation of the cells of the anterior horns. The same view is held by Hunt. The very few cases that have come to autopsy have shown a variety of pathological findings. Saoli found slight degeneration in the upper segment of the cervical cord and a lipoid mass in the dentate nucleus of the cerebellum. Some authors believe that myoclonia is due to irritation of the motor cortex, but they have no autopsies to substantiate such a view. Roger, following Hunt, considers rhythmical myoclonia as a disorder in the striatal system and arrhythmical myoclonia due to a disorder in the spinal cord.

The case described in this contribution suggests strongly an anatomical disorder in the cervical cord. The continuous wave-like muscular contractions associated with fibrillations, also the occasional tonic spasms, all confined exclusively to the flexor and extensor groups of muscles, speak eloquently in favor of a continuous irritation of the segments of the cord innervating those muscles or of the nerves distributed in them, namely the musculo-cutaneous and the musculo-spiral nerves which originate in the fifth and the seventh cervical segments, respectively. Moreover, if we recall the presence at times of "the inversion of the radial reflex" on the left side, which, according to Babinski, is due to a damage of the fifth cervical segment, we are fortified in the assumption that the case under consideration is due to an anatomical disorder in the cervical cord. Babinski has also found that abolition of reflexes in the upper extremities indicates a cord lesion extending from the fifth to the eighth cervical segments.

As to the nature of the lesion in our case it can not be a destruction of the anterior horn cells, as otherwise there would have been muscular atrophy and flaccid paralysis, which are not present. The myokymia is here incessant and continuous. This motor phenomenon is therefore very probably due to an equally incessant and continuous irritation of the cells of the anterior horns or of the anterior roots. It developed soon after a brief preliminary period of paralysis of both upper extremities, following a forced flexion of the head.

CONCLUSION

The case under consideration is one of those very few recorded in the literature, which calls attention to the fact that fractures and displacements of the component parts of the cervical vertebrae, which are easily recognized, are

not the only structural damage requiring prompt intervention. Cases with less dramatic objective manifestations demand equally prompt and serious consideration.

The literature on the subject is meager. Jefferson calls special attention to the fact that in all such cases the injury may be trivial and it is directed against the head, producing extreme forward flexion. In a more recent interesting study Walshe and Ross report six cases, in which the cord symptoms were present, following excessive flexion of the head, and in which at the time of the injury the entire attention was given to the trauma of the head and none to the cervical spine. In their cases the changes in the tendon reflexes were the most conspicuous symptoms, and the roentgenography revealed no fracture or dislocation of the vertebrae, except in one case, in which there was a marked narrowing of the fifth, sixth, and seventh cervical intervertebral spaces.

In the case here reported there was also forced flexion of the neck with violence to the vertex of the head; there was no fracture or displacement of the cervical vertebrae but the intervertebral space between the sixth and seventh was a little wider on the right than on the left side. In addition to the changes in the tendon reflexes there was an unusual cord symptom, which was not observed in the cases recorded in the literature at my disposal: namely a myoclonic phenomenon in the form of myokymia and muscular fibrillation. In instances of apparently minor traumatism to the cervical spine the development of myokymia and its limitation to a distinct muscular group of the upper extremities innervated by the fifth, sixth, and seventh cervical segments indicates organic nerve injury.

BIBLIOGRAPHY

1. UNVERRICHT, PROFESSOR: Ueber familiäre Myoclonie, *Deutsch. Ztschr. f. Nervenhe.*, 1895, vii, 32.
2. LUNDBORG, H.: Ist Unverricht's sogenannte familiäre Myoklonie eine klonische Entität, welche in der Nosologie berechtigt ist? *Neurol. Centralbl.*, 1904, xxiii, 162.
3. POPOFF, N. M.: A special form of myoclonus, *Russk. Vrach.*, 1914, xiii, 965.
4. LENOBLE, E., and AUBINEAU, E.: Le Nystagmus-myoclinie, *Rev. de méd.*, 1911, xxxi, 209.
5. FRIEDREICH, N.: Paramyoklonus multiplex, *Arch. f. path. Anat.*, 1881, lxxxvi, 421.
6. SIOLI, F.: Ueber histologischen Befund bei familiärer Myoklonus Epilepsie, *Arch. f. Psych.*, 1913, li, 30.
7. ROGER, H.: Myoclonia, *Ann. de méd.*, 1922, xii, 150.
8. JEFFERSON, G., and OTHERS: Discussion on spinal injuries, *Proc. Roy. Soc. Med. (Section on Orthopedics)*, 1928, xxi, 21.
9. WALSH, F. M. R., and ROSS, J.: Clinical picture of minor cord lesions in association with injuries of cervical spine: with special reference to diagnostic and localizing value of tendon reflexes of arm (inversion of radial reflex), *Brain*, 1936, lix, 277.

EDITORIAL

THE EXCHANGE OF CHIEFS OF SERVICE

EXCHANGE professorships at universities exist now in all countries, and their advantage is universally recognized. The chief of a hospital service is the analogue in the clinical field of the professor in the academic field. Would there not be many advantages to a system of exchanges of chiefs of services?

Just as a college exchanges professors for a while with some other college, so could a hospital exchange temporarily with another in its city one of its chief physicians or surgeons. A physician responsible for the organization and the conduct of a service in a hospital could thus spend a period of time every once in a while at an institution other than his own, taking over the work of the man for whom he has been exchanged. Osler recommended that a physician take one year out of every five as a sabbatical year, away from his usual work. Most persons, because of economic conditions, cannot absent themselves so long and so often. By means of such exchanges, however, a physician can be brought into completely new hospital surroundings every once in a while, and his associates by their contact with a new chief can also be given the stimulation of a new mental environment. Whether the period of exchange should be a short one, as a month, or a long one as a year, and what the frequency should be with which exchanges are made with another institution, are matters which would have to be decided between the individual hospitals. Some would want to have the periods of exchange made frequently and for long duration, some would deem it best to have the exchanges made but infrequently and for but short periods. There can be no general rule as to what is best for all.

The advantages of such an exchange to the hospitals concerned seem obvious. A hospital service loses the supervision of its chief for but a relatively short time. In return for this loss it has working within its walls a new man, an individual who during his stay will instill many fresh ideas into his new colleagues, both those on his own immediate staff, and those in other departments whom he meets as a result of consultations. In the course of years in all institutions certain procedures become routine and almost a habit. It is a natural tendency of man to get into a rut of routine, and once in such a rut he is apt to become slipshod in his work. With the introduction of a new chief the old routines and ideas are brought into review and inevitably compared with procedures and beliefs current in other places, and as a result of this reëxamination all profit, the staff of the hospital, the routine of the hospital, and medical relations in the city at large.

Provincialism, the feeling that the members of one's own hospital are the only ones well versed in medicine and the various specialties, will be overcome as the work of men from other places is seen and found good.

Esprit de corps will not be limited to the confines of one's own institution but will tend to spread and include the members of the hospitals with which exchanges are being made; and finally perhaps some day all physicians of the city will feel towards one another that same respect, friendship, and intimacy, that they now have for the staff of their own institution. Doctors will learn by direct contact and observation the special abilities not only of the men in their own group but the particular abilities of men in other hospitals in that locality.

The exchange physician will frequently find that his new associates are especially well versed in lines of work with which he has not been particularly concerned up to now. Thus it may be that they are especially skilled in gastroscopy or in the study of arthritis. His own special interests in the past may have been along different lines. In such cases he cannot but learn and profit from his contact with these younger men on his staff. He will not be giving them his experience without receiving a fair return. Perhaps he will find in his new hospital several junior physicians expert in some particular line of work, for instance parasitology, which may be quite an undeveloped field in his own institution, and he could well request permission to take back with him to his hospital one of this group, to the benefit of the young man and to the benefit of the institution to which that young man is transferred. On the other hand, the exchange physician may be especially interested in something which is studied and treated but little at his new place of work. Thus, for instance, he may be an authority on tuberculosis, and as a result of his presence and stimulation a whole new field may be opened up to and developed by the men with whom he now comes in contact.

The plan here presented is not entirely new. At the Peter Bent Brigham Hospital in Boston a step in this direction has already been made, in that for some time past it has been customary there for men unconnected with the institution to be invited to act as Attending Physicians pro tem., and to conduct rounds for a period of two weeks or so. What has been done at Peter Bent Brigham is excellent. It is capable of widespread application.

I. H. MARCUS.

REVIEWS

Physical Diagnosis. By RICHARD C. CABOT, M.D., and F. DENNETTE ADAMS, M.D.
12th Ed. 846 pages; 16 × 23.5 cm. Williams and Wilkins Co., Baltimore.
1938. Price, \$5.00.

The twelfth edition of Cabot's *Physical Diagnosis*, published by Richard C. Cabot and F. Dennette Adams, shows many changes from the earlier editions. These were strongly marked with the personality of the author and based to a great extent on his personal experience. In the preparation of the present volume a large number of specialists drawn principally from Cabot's colleagues in the Massachusetts General Hospital have collaborated. Such a development has manifest advantages and will probably add to the popularity of this well known text.

No field of physical diagnosis has been neglected and all are well presented. The many new photographs and roentgen-ray pictures deserve note because of their careful selection and excellent reproduction without loss of detail. The diagnostic charts are valuable.

There is an adequate and well balanced chapter on elementary electrocardiography and another new chapter on the nervous system which is excellent.

In brief, the new edition has retained the greater part of the value of the older text and shows many new features which will greatly help the modern medical student.

R. B. M., JR.

Trauma and Disease. Edited by LEOPOLD BRAHDY, B.S., M.D., and SAMUEL KAHN, B.S., M.D. 613 pages; 14 × 23 cm. Lea and Febiger, Philadelphia. 1937.

An exceptionally well selected group of contributors has enabled the editors to present a picture of the relation of trauma to disease which is of great interest to all internists. To those physicians who are concerned with the determination of compensation for trauma it will be invaluable.

There is a very sane introductory chapter by the two editors, in which the requisites for allocating a causative rôle to trauma are analyzed. This is followed by chapters on the relation of trauma to heart disease, peripheral vascular disease, pulmonary disease, gastrointestinal disease, genito-urinary disease, obstetric and gynecologic conditions, mental disorders, neurosyphilis, diseases of the nervous system, of the bones, of the joints, of the spine, neoplasms, diabetes, thyroid disease, and septicemia.

The bibliography is arranged topically and placed at the end of each section. Most of the authors present valuable articles from the foreign literature which is on the whole richer in this field than our own.

The method of treatment of the subject, as might be expected, varies in the different chapters. The chapter on the relation of trauma to the diseases of joints, for example, approaches the problem in a broad theoretical manner which however interesting it may be will not be of great help in connection with the analysis of the rôle of trauma in an individual instance. In contrast the discussion of the effect of trauma on disease of the spine is admirably specific and fortified by case citations and brief summaries of the author's conclusions.

All in all, this monograph is a very valuable contribution in a difficult field and every internist who consults it will wish to have a copy on his own shelves.

M. C. P.

Crystalline Enzymes. By JOHN H. NORTHROP. xv + 176 pages; 16 × 23.5 cm. Columbia University Press, New York. 1939. Price, \$3.00.

This excellent monograph is based on a series of lectures on the isolation and chemistry of the proteolytic enzymes and bacteriophage, which were given at Columbia

University in 1938. Although the historical development of the subject has been given adequate attention it is primarily a review of the author's own experimental work.

The contents consist of seven chapters devoted, respectively, to the general chemistry of enzymes; pepsin; pepsinogen; chymo-trypsinogen and chymo-trypsin; trypsinogen, trypsin and trypsin-inhibitor; carboxypeptidase; bacteriophage, and finally, an appendix containing detailed directions for the preparation and crystallization of the enzymes.

The book is written in a very interesting manner and contains many valuable tables. The photomicrography of the crystalline enzymes is particularly excellent.

E. G. S.

The New-Born Infant. By EMERSON L. STONE, M.D. 291 pages; 20.5 × 13.5 cm. Lea and Febiger, Philadelphia. 1939. Price, \$3.00.

The purpose of this publication is expressed in the preface: "The death rate of infants from seven days to one year of age, in the United States registration area, has been reduced 53 per cent during the years of 1916 to 1934 inclusive. During the same time the death rate of infants under seven days of age has been reduced only 10 per cent." Naturally any work concerned with furthering a reduction in infantile mortality is of interest to the obstetrician, pediatrician and general practitioner.

The author has devoted himself extensively to the physiology, the development and the medical care of the newly born infant. Such pertinent subjects as injuries attendant upon delivery and infections and disorders of the special systems receive full attention.

The entire manual is well organized, presenting conflicting views in an unbiased fashion. The work is short and yet without any serious omissions. At times the author seems to overstep his scope, especially when discussing feeding.

There are excellent bibliographical references included.

The book is unreservedly recommended for the student, obstetrician, pediatrician, and general practitioner.

J. E. B.

Recipes and Menus for Allergics: A Cookbook for the Harassed Housekeeper. By MYRA MAY HAAS, and NATHAN SCHAFER, M.D.; Menus by CAY HILLEGAS, B.S. 250 pages, 7 drawings; 20.5 × 14 cm. Dodd, Mead and Company, New York. 1939. Price, \$2.50.

The task of preparing diets for an allergic, who must avoid one or more foods, is no sinecure, as anyone who has attempted it will readily agree. This is an especially formidable undertaking when such basic dietary elements as wheat, eggs or milk must be withheld and unfortunately, they are among the more common offenders. The authors would seem to have succeeded rather well.

In the preface, a brief but good explanation of the meaning of allergy is given; also, there is a listing of certain substances as cottonseed, cereals and spices with comments upon the many food products of which they may be constituents. In addition, the content of mixed foods as sauces and dressings, beverages and flavorings and colorings are discussed.

The diet section is divided into eight parts: egg allergy, milk allergy, wheat allergy and combinations of these. The final section has to do with miscellaneous food allergies such as coffee, fish and spices.

Seven of the sections are preceded by amusing drawings by Soglow which are a real addition to the text.

In the reviewer's opinion, the book should be most helpful to both patient and physician when allergic elimination diets are indicated.

H. M. B.

COLLEGE NEWS NOTES

NEW LIFE MEMBER

Dr. Clarence L. Hyde, F.A.C.P., Akron, Ohio, became a Life Member of the American College of Physicians on May 31, 1939.

GIFTS TO THE COLLEGE LIBRARY

Acknowledgment is made, with appreciation, of the receipt of the following donations to the College Library of publications by members:

Books

- Dr. Richard M. Burke (Associate), Sulphur, Okla., "A Historical Chronology of Tuberculosis";
Rear Admiral Charles S. Butler, F.A.C.P., (MC), U.S.N., "Syphilis Sive Morbus Humanus: A Rationalization of Yaws So-Called" (College Edition).

Reprints

- Dr. Mitchell Bernstein, F.A.C.P., Philadelphia, Pa.—6 reprints;
Dr. J. Lewis Blanton, F.A.C.P., Fairmont, W. Va.—1 reprint;
Dr. Samuel Blinder (Associate), New York, N. Y.—1 reprint;
Dr. William J. Bryan, Jr., F.A.C.P., Tulsa, Okla.—1 reprint;
Dr. Richard M. Burke (Associate), Sulphur, Okla.—1 reprint;
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 Dr. Bernard Langdon Wyatt, F.A.C.P., Tucson, Ariz.—7 reprints;
 Dr. L. S. Ylvisaker, F.A.C.P., Newark, N. J.—1 reprint.

Acknowledgment is also made of the gift by Dr. O. Costa Mandry, F.A.C.P., San Juan, P. R., of the bound numbers of the Bulletin of the Department of Health of Puerto Rico, Volumes I, II, and III, containing contributions by several members of the College.

Dr. William Gerry Morgan, F.A.C.P., Historian of the College, presented for the College Archives a photograph of a formal luncheon of Officers of the College and selected guests, given during the Montreal Annual Session of the College by Dr. J. E. Dubé, F.A.C.P. Dr. Morgan also donated to the College twenty-eight volumes from his personal library, including among others the following:

Cyclopedia of American Medical Biography, I & II—Howard A. Kelly;
 Notes on Chemical Lectures—John Marshall;
 The Mechanism of the Heart and Its Anomalies—Emilie Geraudel, translated by Louis F. Bishop, Sr., F.A.C.P., and Louis F. Bishop, Jr., F.A.C.P.;
 Lambe on Cancer—William Lambe (1809);
 Life and Letters of Dr. William Beaumont—Jesse S. Myer;
 Mechanisms of Character Formation—William A. White;
 The Destiny of Man—John Fiske;
 The Memoirs of a Physician—Alexandre Dumas.

AMERICAN BOARD OF INTERNAL MEDICINE EXAMINATIONS

The next written examination by the American Board of Internal Medicine is scheduled for October 16, 1939, to be given in various centers. For specific information address the Secretary-Treasurer, Dr. William S. Middleton, 1301 University Ave., Madison, Wis.

Dr. Walter E. Vest, F.A.C.P., Huntington, W. Va., President of the Southern Medical Association, received the honorary degree of Doctor of Science at the recent Commencement Exercises of the Medical College of Virginia.

At the recent meeting of the Society for Clinical Investigation held at Atlantic City, N. J., Dr. E. M. Landis, F.A.C.P., Phillips Medalist of the College, was appointed Secretary. Dr. J. Q. Griffith (Associate), Philadelphia, was elected a member of the Society.

Dr. Herbert T. Kelly, F.A.C.P., Philadelphia, Pa., addressed a joint meeting of the Lackawanna County Medical Society and the Scranton Dietetics Society, in Scranton, on Tuesday, April 18, 1939, on "Deficiency Disease with Special Reference to Vitamins."

Dr. Conley H. Sanford, F.A.C.P., has been appointed Professor of Medicine and Chief of the Division of Medicine in the College of Medicine of the University of Tennessee, effective July 1, 1939. Dr. Sanford also becomes Chief of Staff of the John Gaston Hospital as of the same date.

Dr. Theodore F. Bach, F.A.C.P., Associate in Medicine, University of Pennsylvania Graduate School of Medicine, spoke before a Seminar of The Hazleton Branch of the Luzerne County Medical Society, Thursday, May 18, 1939, on "Diagnostic Points of Value, together with, Treatment of Arthritis with Methods Available to the General Practitioner."

On January 11, 12, and 13 of the current year, the Rochester Academy of Medicine, under the Presidency of Dr. David B. Jewett, dedicated its new home. Among the honorary guests were distinguished physicians and surgeons from all parts of the United States and Canada. President Jewett presided at the Dedicatory Meeting, the Dedicatory Dinner, and the Public Meeting. Dr. William A. Groat, F.A.C.P., President of the Medical Society of the State of New York, and Dr. Logan Clendenning, F.A.C.P., Kansas City, Mo., were among those presenting addresses.

At the recent annual meeting of the Gastro-Enterological Association the following officers were elected for the coming year: President, Dr. Irvin Abell, Louisville, Ky.; First Vice-President, Dr. Andrew C. Ivy, F.A.C.P., Chicago, Ill.; Second Vice-President, Dr. Russell S. Boles, F.A.C.P., Philadelphia, Pa.; Secretary, Dr. Albert F. R. Andresen, F.A.C.P., Brooklyn, N. Y.; Treasurer, Dr. A. H. Aaron, F.A.C.P., Buffalo, N. Y.; Recorder, Dr. Sara M. Jordan, F.A.C.P., Boston, Mass.; Members of the Council, Dr. Chester M. Jones, F.A.C.P., Boston, Mass., Dr. Ralph C. Brown Chicago, Ill., and Dr. Ernest H. Gaither, F.A.C.P., Baltimore, Md.

The next meeting of the Association will be held June 10-11, 1940, at the Hotel Claridge, Atlantic City, N. J.

The Twelfth Graduate Fortnight of the New York Academy of Medicine will be held October 23 to November 3, 1939, on the subject of "The Endocrine Glands and Their Disorders." The program will comprise Afternoon Clinics, Evening Meetings, Morning Round Table Conferences, and Scientific Exhibits. The registration fee for non-members is \$5.00. Among the invited speakers on the Evening Sessions program appear: Dr. J. B. Collip, F.A.C.P., Montreal, "Physiology of Anterior Lobe of Pituitary Gland"; Dr. Elmer L. Sevringhaus, F.A.C.P., Madison, Wis., "Therapeutic Application of Female Sex Hormones"; Dr. David Marine, F.A.C.P., New York, N. Y., "Physiology and Principal Inter-relations of the Thyroid"; Dr. James H. Means, F.A.C.P., Boston, Mass., "Hypothyroidism"; Dr. Robert F. Loeb, F.A.C.P., New York, N. Y., "Adrenal Insufficiency"; and Dr. B. S. Oppenheimer, F.A.C.P., New York, N. Y., "The Cushing Syndrome. Neoplasms of the Adrenal

Gland." Program and Registration folders may be obtained from the Secretary, 2 East 103rd St., New York, N. Y.

Lt. Col. A. Parker Hitchens, F.A.C.P., of the Medical Corps, U. S. Army, has been appointed to head the Department of Public Health and Preventive Medicine at the University of Pennsylvania School of Medicine, Philadelphia, Pa. In addition to directing this Department, Col. Hitchens will become the George S. Pepper Professor of Public Health and Preventive Medicine.

Col. Hitchens graduated from the Medico-Chirurgical College of Philadelphia in 1898, and for a number of years was connected with the H. K. Mulford Laboratories. From 1925 to 1929 he was technical adviser in public health and sanitation on the staff of Gen. Leonard Wood in the Philippines. More recently, Col. Hitchens has been assistant professor of military science and tactics at the University of Pennsylvania.

At a recent meeting of the American Medical Association, Dr. Rock Sleyster, F.A.C.P., Wauwatosa, Wis., was inducted as President, Dr. Nathan B. Van Etten, F.A.C.P., New York City, was elected President-Elect, and Dr. Alphonse McMahon, F.A.C.P., St. Louis, was elected Vice-President.

The program of the Third Annual Tuberculosis Seminar of Asheville, N. C., July 10-16, 1939, shows the following participation by Fellows of the American College of Physicians: Dr. Karl Schaffle, F.A.C.P., Asheville, Chairman of the Seminar; Dr. William Ray Griffin, F.A.C.P., Asheville, Address of Welcome; Dr. A. B. Craddock, F.A.C.P., Asheville, "The Minute Anatomy of the Lung and the Development of the Tubercle (Illustrated)"; Dr. Charles H. Cocke, F.A.C.P., Asheville, "History, Symptoms and Examination of the Patient" and "The General Principles of Medical Treatment"; Dr. S. M. Bittinger, F.A.C.P., Black Mountain, "Demonstration of Artificial Pneumothorax, Under Fluoroscopic Control"; Dr. Walter R. Johnson, F.A.C.P., Asheville, "Tuberculosis of the Gastro-Intestinal Tract"; Dr. Paul H. Ringer, F.A.C.P., Asheville, "The Selection of Patients for Collapse Therapy (Illustrated)" and "Non-Tuberculous Pulmonary Diseases (Illustrated)."

Dr. Bradford J. Murphey, F.A.C.P., Director of the Child Guidance Clinic at Wilkes-Barre, Pa., received the honorary degree of Doctor of Science at the Colorado College Commencement, recently.

Dr. Walter C. Alvarez, F.A.C.P., Rochester, Minn., addressed the Section on Gastroenterology of the Medical Society of New Jersey at its 173rd Annual Meeting, at Atlantic City, June 8, 1939, on "The Constitutionally Inadequate Patient." Dr. Manfred Kraemer, F.A.C.P., Newark, N. J., retired as the Chairman of this Section and Dr. Hyman I. Goldstein (Associate), Camden, N. J., retired as the Secretary of this Section and was elected Chairman. The New Jersey Medical Society is the oldest medical society in America.

Erwin F. Faber, anatomical artist and instructor in pathological drawing at the University of Pennsylvania School of Medicine, died during May of a heart attack

at his home in Philadelphia. His illustrations for important medical works are widely known to the medical profession.

A REQUEST FOR SUGGESTIONS

In the Board Room of the College Headquarters, 4200 Pine Street, Philadelphia, there is a wall space above the mantle, 43 inches broad and 36 inches high, which offers a splendid opportunity for an original painting or etching.

The Board Room is finished in oak paneling and the proposed painting will be the highlight of the room.

The House Committee desires suggestions from the membership at large in order that an appropriate and dignified work of art may be selected. One subject might represent some event in the development of medicine, preferably occurring in North America. Another possibility might be found in some historical event of importance in connection with the origin and growth of The College.

The House Committee will appreciate suggestions regarding the type and subject of the proposed picture. It will also be receptive to offers from any member who desires to underwrite same.

Communications should be addressed to the Chairman of the House Committee, Edward L. Bortz, M.D., 2021 W. Girard Avenue, Philadelphia, Pennsylvania.

SPECIAL MEETING OF THE BOARD OF REGENTS

Joint Conference Between the Board of Regents of the American College of Physicians and the Board of Trustees of the American Medical Association

At the invitation of the Board of Trustees of the American Medical Association a joint conference between that Board and the Board of Regents of the American College of Physicians was held at Chicago, April 29, 1939, at which there was an extended discussion of graduate, postgraduate, and continuing medical education and a detailed review of the activities of the Council on Medical Education and Hospitals of the American Medical Association. Following the conference there was a special meeting of the Board of Regents at the Drake Hotel, Chicago, at which resolutions were adopted, (1) instructing Dr. Hugh J. Morgan, as Chairman of the Committee on Postgraduate Education of the College, to attend a joint session of the Council on Medical Education and Hospitals and representatives of the American Board of Internal Medicine at St. Louis on May 14, 1939, and (2) appointing the Committee on Postgraduate Education of the College, consisting of Drs. Hugh J. Morgan, Charles Sidney Burwell, Joseph A. Capps, Charles H. Cocke, and William J. Kerr, to meet and confer with the Council of Medical Education and Hospitals of the American Medical Association, or a committee from this organization, for the discussion and formulation of principles and plans for the further development of graduate medical instruction.

Other items of business transaction by the Board of Regents included an announcement from President O. H. Perry Pepper that Dr. Howard T. Karsner of Western Reserve University School of Medicine had accepted the appointment as General Chairman of the 1940 Annual Session, Cleveland, of the College and that the official date would be April 1-5, 1940. Dr. Karsner had already proceeded with the tentative appointment of committees and other general arrangements. Hotel

Statler has been selected as the official Headquarters Hotel, but General Sessions and Round Tables will be conducted in the public auditorium.

Dr. William D. Stroud, Treasurer, presented the following additions required for the 1939 operating budget of the College, which upon resolution were approved:

Counsel Fee, House Committee's appeal for exemption from real estate taxes on	
College Headquarters	\$ 167.35
New typewriter for Editor's office	93.56
Additional appropriation for traveling expenses of guest speakers, New Orleans	
Session, President's budget	750.00
Total	\$1010.91

Treasurer Stroud also pointed out that there may develop the necessity for an additional appropriation to cover expenses of the Ladies Entertainment Committee, New Orleans Session, because the College budget was prepared with the supposition that there would be only 250 visiting ladies, whereas 578 were registered. There was a general discussion concerning the ladies entertainment for future Annual Sessions of the College and the consensus of opinion was that these programs should be less elaborate in the future. A resolution was adopted providing that the Treasurer and the Executive Secretary be authorized to pay any proper bills that may be received for the ladies entertainment at the New Orleans Session, should the present appropriation be inadequate.

The President was directed to communicate to the American College of Surgeons a report that the American College of Physicians has been carrying on conferences and appointing representatives, but has taken no decisive action on its future policy with regard to the problem of graduate and postgraduate medical education.

On the recommendation of the Committee on Public Relations, presented by Dr. James E. Paullin, Chairman, resignations of Dr. Charles S. Greene (Associate), Canton, Ohio, and Dr. Ralph Henry Kuhns (Associate), Chicago, Ill., were accepted. Likewise by resolution, action was taken concerning the remittance of dues of a Fellow who had retired from practice because of illness, and a hearing of another Fellow concerning discipline. The Secretary General, Dr. George Morris Piersol, reported the following deaths since the last meeting of the Regents:

Dr. Alfred Stengel, Master, Philadelphia, Pa., April 10, 1939;

Dr. Amos Henry Stevens, Fellow, Fairmont, W. Va., March 12, 1939.

Dr. Piersol reported that Dr. Alexander G. Brown, Jr., of Richmond, Va., had become a Life Member of the College.

President Pepper called upon members of the Board of Regents either to volunteer to give papers personally at the next Annual Session or, by letter, to suggest the most competent men who might be obtained as speakers. He also asked for suggestions of general topics that may have been neglected in recent years, also suggestions for the Convocation orator.

The meeting adjourned with all Officers and Regents standing in silent tribute to the memory of Dr. Alfred Stengel.

MINUTES OF THE BOARD OF GOVERNORS

New Orleans, La., March 27, 1939

A regular meeting of the Board of Governors of the American College of Physicians was held at New Orleans, March 27, 1939, with Dr. Charles H. Cocke presiding as Chairman, and Mr. E. R. Loveland acting as Secretary, and with the following present: Dr. Oliver C. Melson, Dr. Ernest H. Falconer, Dr. Fred M. Smith, Dr. W. S. Kerlin (representing Dr. J. E. Knighton), Dr. Henry R. Carstens, Dr. A. Comingo Griffith, Dr. Clarence L. Andrews, Dr. Charles H. Cocke, Dr. Julius O. Arnson, Dr. Alexander M. Burgess, Dr. Paul K. French, Dr. J. Morrison Hutcheson, Dr. Charles E. Watts, Dr. Walter E. Vest, Dr. Hugh A. Farris, Dr. Joseph Kaufman (representing Dr. Charles F. Moffatt), Dr. Fred W. Wilkerson, Dr. Fred G. Holmes, Dr. Lewis B. Flinn, Dr. Turner Z. Cason, Dr. James G. Carr, Dr. C. W. Dowden, Dr. Eugene H. Drake, Dr. Henry M. Thomas, Jr., Dr. Louis H. Fligman, Dr. LeRoy S. Peters, Dr. Charles F. Tenney, Dr. A. B. Brower, Dr. Homer Rush (representing Dr. T. Homer Coffen), Dr. M. D. Levy, Dr. James F. Churchill, Dr. James J. Waring, Dr. Francis G. Blake, Dr. Samuel E. Munson, Dr. Robert M. Moore, Dr. Thomas Tallman Holt, Dr. William B. Breed, Dr. Warren Thompson, Dr. Leander A. Riely, Dr. Nelson G. Russell, Dr. Edward L. Bortz, Dr. John L. Calene, Dr. J. Owsley Manier, Dr. Louis E. Viko, Dr. Arthur Duryea (representing Dr. Harry L. Arnold), Dr. J. Howard Holbrook, and Dr. Thomas Parran.

Chairman Cocke announced that proper credentials as Alternates had been presented by Dr. W. S. Kerlin, of Louisiana, Dr. Joseph Kaufman, of the Province of Quebec, Dr. Homer Rush, of Oregon and Dr. Arthur Duryea, of Hawaii, and that in accordance with the By-Laws they were properly seated with all rights and privileges of Governors.

The Secretary read abstracted Minutes of the preceding two meetings of the Board of Governors held in New York City during 1938, which were approved with the correction that Dr. C. W. Dowden had been elected Vice Chairman of the Board of Governors and not "reelected."

Chairman Cocke addressed the Board of Governors, calling to their attention that the subject for particular consideration by the Governors and Regents at the current meeting was that of postgraduate instruction, referring also to the joint meeting and dinner of the Regents and Governors, the night preceding at the Roosevelt Hotel, New Orleans.

The Secretary read communications from various Governors who were unable to be present, and reported that Dr. J. E. Knighton, Governor for Louisiana, had been prevented from coming because of the tragic death of his son.

On motion by Dr. Walter E. Vest, seconded and regularly carried, it was

RESOLVED, that the Secretary immediately dispatch a message of sympathy to Dr. J. E. Knighton from the Board of Governors.

At the request of Chairman Cocke, the Secretary distributed the report of the Committee on Credentials on candidates for Fellowship and Associateship, and the action of the Board of Regents in regard to their election. Full lists of those recommended were passed among the Governors for reviews. The Secretary reminded the Governors that the By-Laws and regulations of the Regents state that proposals and material must be filed thirty days in advance of election, so that the Credentials Committee may have adequate time to complete its work.

Chairman Cocke supplemented the Secretary's remark in regard to the thirty-day rule, emphasizing its importance and the impossibility of the Credentials Committee acting upon proposals that arrive late, and for which there has not been adequate time to collect the prescribed data. Chairman Cocke also emphasized the

importance of Governors writing full and detailed letters in connection with the endorsement of candidates. The Credentials Committee must know why the Governor feels the candidate is qualified, and data should be given in detail, both from the personal and professional standpoints.

The Secretary, Mr. Loveland, was then called upon to present the list of Associates who would be automatically dropped from the Roster because of failure to qualify for Fellowship within the five-year period, in accordance with the By-Laws. Not only was a mimeographed list, with the names alphabetically arranged, presented to each Governor, but each case was discussed, so that the Governors would be fully informed. Eighty-two per cent of those elected to Associateship five years previously had qualified for Fellowship.

Chairman Cocke predicted that any of these men who had completed their five-year Associate term and who may later have adequate credentials for Fellowship may be proposed directly for Fellowship, credit to be given by the Credentials Committee for their five-year Associate term already completed.

Dr. Cocke also reported that the Regents had instructed the Credentials Committee to draw up a new booklet, outlining the requirements, and to more specifically and clearly state the requirements.

On questions propounded by Dr. Thomas T. Holt, Chairman Cocke advised that while a favorable amount of credit is at present being extended for certification by the American Board of Internal Medicine, the Credentials Committee has no right to exempt any candidate for Fellowship from the regular requirements of the Constitution and By-Laws. However, Dr. William B. Breed, Governor for Massachusetts, and a member of the Credentials Committee, stated that modification of the requirements was under consideration by the Board of Regents.

The Secretary, Mr. Loveland, then presented a mimeographed list of Fellows and Associates who were delinquent in dues for two or more years, and who, according to the By-Laws, were subject to being dropped from the Roster. The Governors were asked to scrutinize the list and to communicate with any members in their respective territories, if they felt such members should be further encouraged to retain their memberships—a period of sixty days' grace would be extended to these men by the Board of Regents.

Chairman Cocke announced to the Board of Governors that since the last annual meeting, there had been lost through death 29 Fellows and 4 Associates; that there had been added to the Life Membership Roster, 16, bringing up the total to 117 Life Members of which 8 have died since original subscription, leaving a balance of 109.

The Secretary reported, at the request of the Chairman, that the membership Roster showed

2 Masters
3,027 Fellows
1,202 Associates
<hr/>
4,231 Total

Chairman Cocke made a report on the Postgraduate Courses offered under the auspices of the College during the two weeks just preceding the current Annual Session; 2 Courses given in Baltimore, 2 Courses in St. Louis and 1 Course in Chicago. Two of the scheduled Courses in Chicago and one Course in Nashville had to be cancelled because of inadequate registration. The Courses given had proved very popular, with a total attendance of 118. Indications were that members want specific, intensive courses in the particular branches in which they are interested, rather than general courses. Dr. Cocke suggested that the Board of Governors might assume as one of its functions the investigation through members in their

respective districts of the desires and needs of the members in regard to the type of courses to be offered next year. It was brought out in the discussion that there was a slight increase in the number of members who registered for the Postgraduate Courses for 1939 over the number who registered for the courses in 1938. The registration showed that members came from thirty-four States of the United States, from Canada and Hawaii.

Dr. Henry M. Thomas, Jr., Governor for Maryland, discussed the two Courses given at Baltimore under the organization and leadership of Dr. Pincoffs. He expressed the opinion that the College could profit from year to year by more carefully studying the experience of the previous years and the experience at the various places where Postgraduate Courses have been given, and he suggested that the College appoint an individual, or committee, to supervise the organization of these courses, giving suggestions for improvement to those offering new courses and to ascertain what courses are preferred. He further suggested that the Secretary mail to each Governor the name or names of College members who pursued these courses from each State.

Chairman Cocke said that Governor Thomas' suggestion would be carried out, but that the Committee on Postgraduate Education of the College would serve as the clearing house for suggestions, for organization, selection and improvement of Postgraduate Courses in the future.

Governor Thomas made the further suggestion that each member of the class each year should be given a complete Roster, including names and local addresses of men taking the courses, so that contacts among the members could be facilitated.

Dr. Fred G. Holmes, Governor for Arizona, opened the discussion as to the possibility of holding Postgraduate Courses at another time of year than just before the Annual Session. It so happens that physicians in the southwest are at the peak of their work in March and April, and it would be far more convenient for them to take the graduate courses later in the spring, or in the early autumn.

Chairman Cocke advised that the members had been carefully canvassed in this regard, and while there were many factors to be considered, including the convenience of the teaching institutions where the courses are given, it had appeared that the period immediately preceding the Annual Sessions suited the largest number of members, although the matter might be further considered with respect to giving two sets of courses, each at different seasons.

Governor Thomas T. Holt, of Kansas, recommended that courses be announced in subjects such as physiology, chemistry and metabolism, in order that a larger number of men might avail themselves of the opportunity of building up knowledge in these subjects, which is so needed. He suggested that where courses are oversubscribed, the teachers might be persuaded to repeat the courses again later in the year.

In the discussion that followed, the following questions were advanced: Do some members utilize these Courses but fail to attend the Annual Session which follows? What influence has the location of the annual meeting exerted on the attendance of graduate courses in cities not in fairly close proximity to the meeting city?

Dr. Hugh A. Farris, Governor for the Maritime Provinces, stated that he had attended one of the courses, but that out of a group of fifteen only about three had come on to the Annual Session.

Dr. A. Comingo Griffith, Governor for Missouri, expressed the opinion that more members would attend the Annual Session if the graduate courses were given in cities nearer the seat of the Annual Session.

Dr. Charles F. Tenney, Governor for eastern New York, reviewed the experience of the New York Academy of Medicine in regard to its Postgraduate Fortnight. The annual Postgraduate Fortnight is usually devoted to some particular subject, such for instance as gastro-enterology, blood dyscrasias or endocrinology. By correlating the work and restricting it to a general subject, the course is very much more intensive.

He advocated that instead of utilizing many cities and scattering the registrants, all the Postgraduate Courses be given in one center, possibly changing the center from year to year. This would concentrate energy and add to the facilities of general contacts.

Dr. James G. Carr, Governor for northern Illinois, and director of the Postgraduate Course in Chicago, reported that several States had been represented in the registration, including Pennsylvania, Idaho, Tennessee, Michigan, Wisconsin, Nebraska, and others. Most of the registrants had intended to attend the Annual Session also. So far as specialties were concerned Dr. Carr advocated a more intensive study to determine what members desire and where they desire them. Those who pursued the courses at Chicago had expressed much pleasure and satisfaction concerning the course.

Dr. Louis H. Fligman, Governor for Montana, suggested the desirability of sending out the announcement of the Postgraduate Courses earlier in the year. Many physicians practice in smaller communities and have to make plans far in advance. They should be able to anticipate and arrange for attendance at these Postgraduate Courses longer in advance.

Dr. William B. Breed, Governor for Massachusetts, suggested that it might properly be made one of the functions of the Board of Governors to consider what the requirements are for admission to Associateship or Fellowship, because the Governors have a more intimate contact with the men who present themselves as candidates, and the suggestions presented by the Governors might be passed on to the Board of Regents and the Credentials Committee for consideration.

Chairman Cocke ordered that this be placed on the agenda for the next succeeding meeting of the Board of Governors, and that the Governors bring to that meeting specific suggestions.

Dr. Breed then asked the Board of Governors to view the commercial exhibits critically. He expressed himself as not being in sympathy with commercial exhibits, and expressed the fear that the College may be becoming too dependent upon income derived therefrom, because the exhibits may interfere with holding meetings of the College in some cities that lack facilities. He pointed out that the net income to the College at the preceding New York Session had been approximately \$14,000.00 and somewhat over \$11,000.00 at the current meeting. His only expressed objections to the commercial or technical exhibits referred to these considerations. However, Dr. Breed asked the Board to consider the possibility of adding a small scientific exhibit, such as conducted by the American Medical Association. He asked that the Board give this subject some thought and present suggestions at the next succeeding meeting.

Chairman Cocke reported that the Board of Regents had already instituted an investigation into all financial matters of the College, including exhibits and advertising, and would later have a report. However, Dr. Cocke requested that the Governors give the matter their careful thought and critical judgment, and bring up the subject again for discussion.

The Executive Secretary distributed complete copies of the financial statements of the College for the year 1938, for the information of the Governors, and offered to answer any questions concerning the same.

Adjournment:

(Signed)

Attest: E. R. LOVELAND,
Executive Secretary

MINUTES OF THE BOARD OF GOVERNORS

New Orleans, La., March 29, 1939

The second meeting of the Board of Governors of the American College of Physicians, held during the Twenty-third Annual Session, occurred on March 29, 1939, at the New Orleans Municipal Auditorium, with Dr. Charles H. Cocke acting as Chairman, Mr. E. R. Loveland acting as Secretary, and with the following present: Dr. Oliver C. Melson, Dr. Ernest H. Falconer, Dr. Fred M. Smith, Dr. W. S. Kerlin (representing Dr. J. E. Knighton), Dr. Henry R. Carstens, Dr. A. Comingo Griffith, Dr. Clarence L. Andrews, Dr. Charles H. Cocke, Dr. Julius O. Arnson, Dr. Alexander M. Burgess, Dr. Paul K. French, Dr. J. Morrison Hutcheson, Dr. Charles E. Watts, Dr. Walter E. Vest, Dr. Hugh A. Farris, Dr. Joseph Kaufman (representing Dr. Charles F. Moffatt), Dr. Fred W. Wilkerson, Dr. Fred G. Holmes, Dr. Lewis B. Flinn, Dr. Turner Z. Cason, Dr. James G. Carr, Dr. C. W. Dowden, Dr. Eugene H. Drake, Dr. Henry M. Thomas, Jr., Dr. G. W. F. Rembert, Dr. Louis H. Fligman, Dr. LeRoy S. Peters, Dr. Charles F. Tenney, Dr. A. B. Brower, Dr. Homer Rush (representing Dr. T. Homer Coffen), Dr. James F. Churchill, Dr. James J. Waring, Dr. Francis G. Blake, Dr. Robert M. Moore, Dr. Thomas Tallman Holt, Dr. William B. Breed, Dr. Warren Thompson, Dr. Leander A. Riely, Dr. Edward L. Bortz, Dr. John L. Calene, Dr. J. Owsley Manier, Dr. Louis E. Viko, Dr. Arthur Duryea, Dr. J. Howard Holbrook, Dr. Thomas Parran, Dr. Nelson G. Russell.

The Secretary read abstracted Minutes of the preceding meeting, which were approved as read.

Chairman Cocke reported that at a meeting of the Board of Regents on March 28 various matters referred by the Board of Governors had been taken under consideration. Furthermore, the Regents had instituted an intensive study of exhibits, fees and dues and all other matters affecting the finances of the organization. Dr. Cocke also reported that the Board of Regents had adopted a resolution requesting the Board of Governors to appoint a committee to act in an advisory capacity to secure information and to suggest regulatory principles concerning the postgraduate course program. This committee is to make a canvass and study of the situation with regard to location, time and other factors, with a view to making the courses further effective. The findings and recommendations of the committee shall be placed at the disposal of the Committee on Postgraduate Education of the College.

Dr. Thomas T. Holt, Governor for Kansas, reported that he had contacted all the members from his locality who had attended the Postgraduate Courses preceding the New Orleans Session, and had determined that they were all highly pleased and grateful for these courses. He advocated that the College should start a memorial library, having distinguished men and teachers give talks—such for instance as Dr. James B. Herrick on coronary thrombosis, as described in his earlier days—and having these talks recorded and placed in the College Library as memorials to these men.

Dr. J. Howard Holbrook, Governor for Ontario, expressed a deep interest in our program for postgraduate education, and predicted that physicians will not be going to Europe to the same extent for postgraduate work as in the past. He suggested that it be the duty of each Governor to see that the Associates in his territory shall be able to qualify as soon as possible for Fellowship. The Governors should always have available the full list of Associates, and they should encourage these men to pursue the Postgraduate Courses made available to them by the College. More Associates would undoubtedly pursue these courses if they were urged to do so by the Governors. He suggested that the Postgraduate Courses might very properly have as one of their chief objects that of qualifying Associates for Fellowship, and that the Credentials Committee should grant specific credit for attendance at Postgraduate Courses. Dr.

Holbrook said that the present is the opportune time for the College to make a real contribution in the field of Postgraduate Education.

Chairman Cocke reported that it is the custom of the Executive Offices to see that every Governor has a full and up-to-date list of all Fellows and Associates of the College, either through the Directory of the College or through additional reports following meetings of the Board of Regents when elections take place. He also said that the Regents were seriously considering the revision of the published requirements for Fellowship, coördinating the new requirements with those for certification by the national certifying boards. It is anticipated, he said, that in the near future certification by one of the national certifying boards shall be a requisite for Fellowship, though there will be other eligibility requirements.

Dr. Hugh A. Farris, Governor for the Maritime Provinces, reported that he had been requested to present a motion, recommending that the Postgraduate Courses be given at another time than the two weeks preceding the Annual Sessions; possibly following the meeting or, perhaps, in November of each autumn. Some members in his territory had contended that giving the courses before the annual meeting detracted from the meeting. Dr. Farris accordingly moved that the College present intensive Postgraduate Courses of one week following the meeting in the city where the meeting is held. The motion was seconded, and Chairman Cocke opened the question for discussion.

Dr. C. F. Tenney, Governor for eastern New York, pointed out that the Annual Sessions are always held in teaching centers, and that he felt the Postgraduate Courses could more advantageously be organized and given following the meetings. He favored a more closely organized unit with all courses being given in the one city under the general supervision of some distinguished man who had remained after the Session to take charge, supervise and coördinate the work. Dr. Tenney went on to describe the Postgraduate Fortnight of the New York Academy of Medicine. Their mornings are free; in the afternoon there are exhibits in the Academy, and these exhibits are one of the most valuable parts of the course. Lectures are given in the evening by men selected from all parts of the United States, Canada or Europe. Each year the Postgraduate Fortnight is devoted to some particular subject, rather than a diversity of subjects. He pointed out also the matter of expense. Members would have but one expense for railroad fare, if the courses were given in the Annual Session city. He also expressed approval of Dr. Holt's suggestion concerning Associates. He felt that their attendance at the Postgraduate Courses would mean far more than their preparation and submission of case histories and autopsies when coming up for Fellowship.

Dr. Fred M. Smith, Governor for Iowa, also was inclined toward feeling that perhaps the Board was overemphasizing the Postgraduate Courses for the Associates. He expressed his respect and confidence "for the man who can go on his own," and he said that the Associate who has to be carried along by the Governor will not make the sort of Fellow the College ought to have. The men who go farthest in medicine to a large extent are their own teachers, he said. They are influenced by meetings and contacts with men, but these things can be overdone. However, he expressed his approval of conducting the Postgraduate Courses following the Session in the same city.

Dr. Thomas Parran, Governor for the U. S. Public Health Service, pointed out that the motion before the Board might tie the hands of the Committee on Postgraduate Education as to the time and place for the courses, and asked Dr. Farris to consent to an amendment, namely, that the proposal of having Postgraduate Courses following the annual meeting be referred to the Committee on Postgraduate Education, rather than making it binding upon that Committee to schedule all of its courses as indicated. He pointed out that there were so many considerations that it did not seem proper for the Board to make a final decision at that time.

Dr. Farris accepted the amendment. Dr. C. F. Tenney pointed out that the Board might be overlooking the fact that in the cities where these meetings are held, the local men for a long time preceding and during the Session have an enormous amount of work to do on the meeting alone, and that all of these extra duties are added to their regular work. He thought it possibly would be a hardship to ask these same men to continue an additional week of postgraduate instruction.

The Secretary, Mr. Loveland, reported that for the preceding year when the Annual Session was held in New York, the Postgraduate Courses in such nearby cities as Boston and Philadelphia were better patronized because the men felt that they would see the best work being done in New York at the Annual Session, and that they would rather take their postgraduate work, therefore, in the nearby teaching centers. There had been fewer who registered for the Postgraduate Courses in New York City than in Boston and Philadelphia.

Dr. A. Comingo Griffith, Governor for Missouri, pointed out that the discussion thus far had shown the many angles to be considered, and no very definite scheme or plan should be adopted too quickly. He favored the Postgraduate Courses being held after the meeting, but that the Committee on Postgraduate Education might well schedule them in near-by cities. This would not necessarily increase the cost of transportation, because railroad tickets are usually good for thirty days, and by utilizing the nearby cities no undue burden would be put upon the local men in the meeting city.

Dr. Alex. M. Burgess, Governor for Rhode Island, urged greater coördination between the courses and through the succeeding years courses should be planned with relation to one another, and the programs coördinated from year to year. He suggested that some of the courses should be given in the autumn.

Chairman Cocke pointed out that the largest medical group in the south, the Southern Medical Association, always holds its annual meeting around the middle of November, and that this would have to be taken into consideration for any meetings scheduled in the autumn.

Dr. Walter E. Vest, Governor for West Virginia, recommended that the Committee on Postgraduate Education should schedule no courses that would interfere with the meetings of the Southern Medical Association.

Dr. Clarence L. Andrews, Governor for New Jersey, asked that the purpose of the Postgraduate Courses be clearly defined. Some men in his State had said they could not take the Postgraduate Courses and attend the Annual Sessions also. He felt that a greater premium should be placed upon attendance by the Associates at the Postgraduate Courses than at the Annual Sessions, and that certain credit for attendance at these courses be extended to all Associates when their credentials are presented for Fellowship.

Dr. J. Morrison Hutcheson, Governor for Virginia, referred back to the motion before the Board, and Dr. Farris informed him that the idea of the motion was that all Postgraduate Courses be scheduled following the meeting, and all other courses be suspended. Dr. Hutcheson reported that in his conversation with Associates, he had found that they felt the Postgraduate Courses in nearby medical centers had been most agreeable to them. He thought it a worthy objective to prevent any conflict of these courses with the annual meetings, and he was unfavorable to discontinuing all courses except those that could be given at the annual meeting city.

Dr. C. W. Dowden, Governor for Kentucky, expressed serious doubt whether the College should sponsor the courses at all. He felt that members may substitute attendance at the courses in place of going to the annual meetings, and that the annual meetings in themselves are the best postgraduate courses that members can obtain anywhere. Men interested in certain branches of medicine can go to the hospitals and see and hear what they want. The comparatively small number of members of the College attending these courses could attend any of the many other courses that

are springing up all over the country. He felt the College is doing entirely too much in this direction, and that these courses are detracting from the Annual Sessions.

Dr. Robert M. Moore, Governor for Indiana, reported that a postgraduate week had been initiated in Indianapolis some years ago, much on the same plan as the New York Postgraduate Fortnight. There is an intensive clinic presentation on all subjects, and outstanding men are brought to conduct the courses. He favored the continuation and promotion of postgraduate work. It is apparent that there will always be some conflicts and that attendance at the Postgraduate Courses may have some influence on the General Sessions; whether the Postgraduate Courses be given in the autumn or following the annual meetings, there is sure to be some influence on the enrollment of the annual meetings.

Dr. T. Z. Cason, Governor for Florida, reported that there is no medical school in the State of Florida, the nearest medical schools being located at Atlanta, New Orleans and Durham, N. C. For eight years the Florida State Medical Association has scheduled graduate courses for doctors of medicine, and Dr. Cason has been the Chairman. His experience had been that all graduate courses must be directed primarily to general practitioners. Figures cited showed that approximately 10 per cent of the members of the Florida State Medical Association availed themselves of these courses; men are brought in from outside of the State Medical Association for the program; the costs have been kept low, and a registration fee of only \$5.00 has been charged. Heretofore, all the postgraduate work has been directed toward the general practitioner; the first half of the week was for the medical subjects and the second half for the surgical and obstetrical subjects. A new experiment was being tried the current year, with an intensive course on a single subject. He asked that the Committee on Postgraduate Education and the Board of Regents consider the plan of giving credit to Associates taking postgraduate work, suggesting that credit not necessarily be limited to those attending the Postgraduate Courses of the College.

Dr. Henry R. Carstens, Governor for Michigan, reported that in Michigan there is a similar program to that in Indiana and New York, only in a smaller way. It is directed toward the general practitioner, but there are also special courses.

Dr. A. B. Brower, Governor for Ohio, suggested that the Board of Governors should feel a personal responsibility, and that each Governor should send a letter outlining his ideas and suggestions to the committee that shall be appointed by the Board of Governors to survey the situation.

Dr. William B. Breed, Governor for Massachusetts, suggested that inasmuch as the motion had accomplished its purpose in creating wide discussion and review of the postgraduate situation, it be withdrawn without action.

Dr. Farris accepted the suggestion, as did also the seconder, and the motion was withdrawn.

Dr. Lewis B. Flinn, Governor for Delaware, "postgraduate education is an attempt to raise the caliber of medical practice throughout the country; first, perhaps, in regard to the members of the College and then the profession at large. The recent suggestions as far as certification by the American Board of Internal Medicine being made a requirement for Fellowship and the recent changes as far as hospital residencies are concerned go to this end. The Postgraduate Courses which have been discussed are more or less under the wrong momentum, and the details being discussed and worked out, in the wrong direction. Is there not another group, the forgotten group of doctors, the friends of doctors around the large metropolitan and teaching institutions in the more remote district of the country, particularly in the States and communities not in intimate contact with teaching institutions? It is a considerable problem to keep general practitioners and prospective internists abreast of things going on in medicine. I have two or three points for your consideration, but, perhaps, not for action at this time. First, the conduct of courses, such as Dr.

Cason of Florida suggested; second, country clinics, such as are being held in some States in the west and southwest. There is another problem which I should like to mention from a local standpoint in Delaware, namely, medical libraries. Until a few years ago, we had no medical library, but a number of members of the College, although not acting as such, were able to start a medical library, which has proved a splendid thing and a growing organization. Younger men, as they come along, are interested in reading and are trained to some extent to read. In the last two years the number of individuals in the community has doubled, and our efforts are now being directed toward carrying the service of a medical library, State medical library, current periodicals, etc., direct to the younger physicians particularly in the outlying districts. This is worth the effort, and may raise the standards of medical education, particularly in localities without facilities of teaching institutions."

Dr. Hugh J. Morgan, Chairman, Committee on Postgraduate Education: "Members of the Board of Governors, I am grateful for the opportunity of meeting with the Board to state very briefly the objectives that the Committee on Postgraduate Instruction has been concerned with in the two years I have been on the Committee. First, we felt that probably the most important things we had to deal with were in connection with postgraduate training for recent graduates in medicine. The matter of assistant residencies, residencies and Fellowships in medicine to the end that men can become trained in the field of general medicine and allied specialties are our objectives. We have been in difficult situations. There are many agencies interested in this problem. The American Medical Association, Council on Medical Education, the American College of Surgeons which has an intensive postgraduate program, and now ours, as a third major organization.

"In looking for the place to get into this field to do effective work, action has been deferred; as to what to do and where to do it. Even if one knows what one would like to do, he has to determine what places are available where recent graduates can go to get the training if they want to go into the field of Internal Medicine. That part of the problem is one of fact-finding. This is being done by the Council on Medical Education and Hospitals of the American Medical Association. We wonder if we could do it better or they could do it better. There is an Advisory Council on Medical Education, Hospitals and Licensure going into existence. We are concerned with this. That is one phase of the Committee's activities not touched upon in the discussion here, which is an important phase. This has to do with the recent graduates and potential members of the College.

"The other main interest of the Committee has been the subject of discussion here today. I think the divergent points that have been expressed here give an excellent idea how difficult it is to proceed in this field. It is important for us to make up our minds as to what the personnel will be. What group are these courses for, anyway. The College of Physicians is going to organize courses, for whom? Our idea is for our own members or potential members. We feel we have no concern in providing courses for general practitioners or for people interested in specialties not related to our own interests. If they are to be given for the College membership or potential members, that somewhat limits the field of our endeavor. We already give, in our annual meetings, one of the best postgraduate assemblies in the country, if not the best; certainly, in the field of general medicine. If our policies in the last two years, in trying to have general courses, has proved unsound, then we should throw that overboard and direct our attention in the courses of medical specialties.

"The question of time that should be put in our courses and when they should be given; their relation to the annual meeting of the College; the geographical distribution of centers in which to be given; all are points discussed here. It is very pertinent that the idea has been raised that these courses should not be given at all.

Against that is the idea that they are so important that we should employ disciplinary measures to force attendance.

"I think on behalf of the Committee that has been concerned with this problem for two years, I would like to say most that I am personally, and I am sure the Committee feels the same, deeply grateful for this Board interesting itself in this problem. We certainly have needed aggressive interest in considering this problem, in regard to just such questions as have been discussed here today. I think it is an important thing for the future that the Board of Governors will have a Committee to examine these questions and waive pros and cons and sift out of such facts as you are able to assemble, what would seem to be the wisest policies in regard to these courses. I think it is certainly going to mean that the Governors are going to have a viewpoint and I think it is an excellent thing, from the point of view of the College as a whole."

On motion by Dr. A. Comingo Griffith, seconded and regularly carried, it was RESOLVED, that the Board of Governors authorize a Committee on Survey of Postgraduate Education, the Committee to be appointed by the Chairman.

Chairman Cocke appointed Dr. Henry M. Thomas, Jr., Governor for Maryland, as Chairman; Dr. James J. Waring, Governor for Colorado; Dr. Edward L. Bortz, Governor for Eastern Pennsylvania; Dr. James G. Carr, Governor for Northern Illinois; and Dr. Ernest H. Falconer, Governor for Northern California.

Dr. J. Owsley Manier, Governor for Tennessee, expressed the opinion that it will be difficult for this Committee to know what action it shall be best to take. He proposed that Dr. Brower's suggestion of a letter from each Governor to the Committee would be helpful. He, therefore, suggested that the Board of Governors instruct the Committee to communicate tentative plans to the individual Governors.

Dr. Thomas Tallman Holt, Governor for Kansas, suggested that each Governor canvass his State and find what the men want and report such findings to the Committee.

Dr. Walter E. Vest, Governor for West Virginia, spoke from the standpoint of the public health aspect, pointing out that this body had been considering postgraduate education from the Board's standpoint, and that those who need postgraduate education least get it; those who take the courses are those who, in the final analysis, need it least, and the College needs some way of reaching the men in the outlying districts who do not get postgraduate instruction.

Chairman Cocke stated that the usual reports on State and district meetings would have to be omitted because of lack of time, but that reports of these had been published from time to time in the "Annals." He asked the individual members of the Board to give some consideration to entrance requirements to the College. The Credentials Committee may circularize members of the Board to get their suggestions.

Mr. Loveland, the Executive Secretary, asked if the Board of Governors would express any sentiment about the place of the next annual meeting. He reported that invitations had been received from San Francisco, St. Paul, Buffalo, Cleveland and Boston for the 1940 Session, and from Kansas City for the 1941 Session. The meeting place is determined upon by the Board of Regents after careful consideration. He said that the two cities most seriously under consideration for 1940 were Boston and Cleveland. The American Medical Association will hold its 1941 Session in Cleveland.

Dr. A. B. Brower, Governor for Ohio, spoke in favor of the 1940 Session being held in Cleveland. He pointed out that the College had not convened there since 1927, and that inasmuch as Cleveland could not entertain the College in 1941, because of the meeting of the American Medical Association, Cleveland particularly wishes to concentrate on our meeting in 1940. He emphasized Cleveland's splendid physical equipment and geographical location. He also felt that hospital facilities are adequate, and that every coöperation would be received from the medical school, the local

Academy of Medicine and College members. The whole invitation had been carefully and fully discussed with the various members of the hospital staffs and teaching staffs, and full coöperation everywhere had been assured. Furthermore, the College membership in the Cleveland district has been greatly strengthened by the election of several of its outstanding internists, and that from every standpoint, the Cleveland invitation should be seriously considered.

Dr. William B. Breed, Governor for Massachusetts—"It seems that the turn of the wheel is up to Cleveland and Boston. The College met ten years ago in Boston. I should say that 1941 would be just as good a year for Boston. We would welcome you in either year. Apparently, 1941 is out for Cleveland. I think that our invitation would hold just as enthusiastically in 1941 as in 1940."

On motion by Dr. A. M. Burgess, seconded by Dr. A. C. Griffith, and unanimously carried, it was

RESOLVED, that the Board of Governors recommend to the Board of Regents the selection of Cleveland for its 1940 Session.

Following several general announcements concerning meetings, the Board adjourned.

Adjournment:

(Signed)

Attest: E. R. LOVELAND,
Executive Secretary

OBITUARIES

DR. ALEXANDER JOHN MACKENZIE, V.D., B.A., LL.D., M.B.,
F.A.C.P., Lieut.-Colonel (ret.) 48th Highlanders of Canada

Dr. A. J. MacKenzie, President of the Ontario Medical Association, died at his home in Toronto, March 3, 1939, after a short illness.

He became a Fellow of this College in 1926 and prized highly his association with the College.

The second son of the late Peter MacKenzie, federal member for South Bruce, he was born at Lucknow, Ont., 66 years ago. Entering University College in the University of Toronto he studied political science and law, with a group of men who became prominent in political life. He took his Arts degree in political science, graduated in law and in medicine. During his course he took an active part in athletics and for several years played an outstanding game in intercollegiate Rugby. His interest in these activities made him a valued member of the Athletic directorate of the university.

He spent a year as intern in the Toronto General Hospital and in a very short time began practice in Toronto. For nearly thirty-five years he taught in the Faculty of Medicine of his university, and for twenty years was the head of one of the medical services in St. Michael's Hospital, where he gave freely of his time and energy to both university and hospital work, rarely missing a day in his wards.

Soon after graduation he was appointed Physician to Upper Canada College, and two generations of men had the advantage of his supervision and advice in sickness and in health. For over thirty years too he was medical officer of the 48th Battalion (Highlanders) rising to the rank of Lieut.-Colonel in that unit in 1917. The 15th Battalion C.E.F. was recruited from the 48th militia, and as M.O. to the 15th Battalion, he proceeded overseas with the first contingent, spending the first winter amidst the discomforts of Salisbury Plains, and then to France where he saw his men falling about him during the first murderous gas attack launched by the Germans at Ypres in April 1915. Those who survived are proud to recall his devotion to his comrades during the trying days which followed. Later in England, he was O.C. Princess Patricia's Red Cross Hospital at Ramsgate, and on his return to Canada was for some time O.C. Military Hospitals in M.D. No. 6 (Halifax). Later he was consultant in medicine M.D. No. 2. His Medals and decorations were the 1914-15 Star, The British War Medal, the Victory Medal and the V.D., the Colonial Auxiliary Forces Officers Decoration.

A charter member of the Academy of Medicine, Toronto, Dr. MacKenzie served actively on many committees, was chairman of the Section of Medicine in 1922, in 1926 became President, and for seven years served on

council. For many years he was active in the Ontario Medical Association. As Counsellor for District No. 11 he did most valuable work for his profession, devoting much time to his important office; this led him into the administration of medical relief when it was inaugurated in the province. His wise counsel and advice will be much missed by those who have the duty of carrying on this work for the Ontario Medical Association. Elected to the presidency of the Association last year he entered into the duties of his office well equipped in every way to be the guiding hand in its many activities, and he spared neither time nor effort to ensure the success of its undertakings.

He will be sorely missed. He was beloved of his students and no one in the medical profession could be held in greater respect. A medical statesman of the first order he was ever ready to assist in any movement which would make the practice of medicine more generally serviceable to the public.

Besides two brothers and two sisters he is survived by his widow, the former Norma Sutherland, daughter of Hon. R. T. Sutherland, a Justice of the High Court of Ontario, and formerly a Speaker in the House of Commons.

Following a private service in his late residence his body lay in state in St. Andrew's Church until the funeral service at 2 p.m. on Monday, March 6, which was attended by hundreds of his friends from all walks of life, with special representatives from the many organizations with which he had been long associated. Dr. MacKenzie loved the simple things of life and the funeral service was typical of his disposition. The ceremony was short and minus an address of eulogy.

Dr. MacKenzie was borne to his grave in Mount Pleasant Cemetery where, under the flag he had so well served, he was laid to rest with the lament of the bagpipes of his forbears, and the Last Post of the bugler of his well loved regiment.

J. H. ELLIOTT, M.D., F.A.C.P.,
Toronto, Ontario, Canada.

DR. ROBERT LEE FELTS

Dr. Felts was born in York County, South Carolina, November 15, 1870. After graduating from the Carolina Academy, he began pharmaceutical studies, receiving the Ph.G. degree from the Maryland College of Pharmacy and his M.D. degree from the University of Maryland School of Medicine in 1898. His postgraduate studies embraced courses in pediatrics in 1924 and in internal medicine in 1922 and 1926.

During the Spanish American War, he served in the Medical Corps of the Fifth Maryland Regiment, where first began his interest in typhoid fever, which became one of his dominant medical interests, by reason of his wide knowledge of the disease then so prevalent. He was stationed in Manila in the Philippine Islands from 1898 to 1902, and was commanding surgeon at

Fort Sam Houston, Texas, from 1902 to 1906. He settled in Durham in private practice in 1907, and from then until illness incapacitated him, was one of the leading internists of his community.

For many years he was Chief of the Medical Staff of Watts Hospital, Durham, a member of the visiting medical staff of Duke Hospital; Secretary of the Durham County Board of Health from 1925 on, member and ex-President of the Durham-Orange County Medical Society; member and ex-Counselor of the Sixth District of the N. C. State Medical Society; member of the Southern Medical Association; member of the American Medical Association; and Fellow of the American College of Physicians since 1931.

At the time of his death, at his home, from coronary thrombosis, May 27, 1939, he was senior attending physician at Watts Hospital.

His publications on the subjects of pyelitis and pregnancy; neurological sequellae of influenza, chylothorax, acute Hodgkin's disease, and purpura hemorrhagica, indicate the catholicity of his interests.

In June 1904, he married Miss Elizabeth Person Kearney, who died in 1925, surviving which marriage are two daughters, Mrs. Virginia Felts Pickard and Mrs. George L. (Elizabeth Felt) Lyon. November 15, 1928, he married Miss Jessie Alexander, from which union a son survives, Robert Lee Felts, Jr.

A man of very dominating personality and strength of character, Dr. Felts owed his position in his community to those qualities of character and honesty which animated all of his dealings with his fellowman. He was a member and past President of the Kiwanis Club; originated and was Chairman of the Durham Community Chest, 1923-1926; a member of Trinity Methodist Church, and a member of the Board of the American Red Cross. His interest in politics was active, but he still found time in a busy life for constant study and reading of medical literature. His passing leaves a void in the medical circles of his community.

CHAS. HARTWELL COCKE, M.D., F.A.C.P.,
Governor for North Carolina.

DR. SAMUEL ROBERT SLAYMAKER

Dr. Samuel Robert Slaymaker died on May 3, 1939, of carcinoma of the pancreas. Dr. Slaymaker was born in 1864 and received his degree in medicine from Rush Medical College in 1892. He spent his entire professional life in Chicago, where he built up a large practice. For most of his time he was connected in some capacity as a teacher in the Medical Department of his Alma Mater, and for many of his later years he held the title of Clinical Professor of Medicine. He was Associate Attending Physician at the Presbyterian Hospital for many years. He also served as a member of the Attending Staff at the Cook County Hospital for a period of some twenty years. His last term in the Cook County Hospital was

marked by his serving as Chief of the Department of Medicine. For many years he was Attending Physician of the Washington Boulevard Hospital, where he also served as President of the Staff.

Dr. Slaymaker was President of the Chicago Society of Internal Medicine during 1922 and 1923. He was one of the founders of the Chicago Institute of Medicine and took an active interest in this work. He was a member of the Chicago Medical Society for a long period, and was a Fellow of the American Medical Association. He was also a member of the Illinois State Medical Society, the Chicago Pathological Society, the Chicago Society of Industrial Medicine, the Chicago Society of Medical History and an Associate of the American College of Physicians. He was an active member of St. Barnabas Episcopal Church.

The death of Dr. Slaymaker removes from our midst one of the best beloved men in Chicago. Through his contacts with patients, with his fellow practitioners and medical students, Dr. Slaymaker had acquired an exceptionally wide acquaintanceship. Wherever he was known he was accorded not only respect but affection. His students and internes with whom he had contact were especially devoted to him and will retain a grateful memory for the opportunity of having served with one so successful in diagnosis, so accurate in treatment, and so considerate in the care of his patients. Dr. Slaymaker's work was excellently done. His memory will be cherished as much for his genial, kindly personality as for the work he did in professional ways.

JAMES G. CARR, M.D., F.A.C.P.,
Governor for Northern Illinois.

DR. BYRON HUBBARD JACKSON

Dr. Byron Hubbard Jackson of Scranton, Pennsylvania, a Fellow of the American College of Physicians since 1934, died May 16, 1939.

Dr. Jackson was born in Kingston, Pa., September 22, 1873, and graduated from the Baltimore Medical College in 1898. He was engaged in general practice until 1908, from which time he followed the specialty of roentgenology exclusively.

Dr. Jackson held the following positions: Roentgenologist, State Hospital of Northeast Pennsylvania, 1908-26; Roentgenologist, Moses Taylor Hospital, 1908 to date; Roentgenologist, Hahnemann Hospital 1917-33; Roentgenologist, West Side Hospital, 1917 to date; Roentgenologist, St. Mary's Kellar Memorial Hospital, 1920 to date; Roentgenologist, West Mountain Sanatorium and Pennsylvania State Tuberculosis Clinic, 1916 to date.

Dr. Jackson was the author of several published papers.

Dr. Jackson was a member of the Lackawanna County Medical Society, The Pennsylvania State Medical Society, American Medical Association,

American Roentgen-Ray Society, Radiological Society of North America (ex-President), Pennsylvania Radiological Society, Central New York Roentgen-Ray Society, Philadelphia Roentgen-Ray Society, Lehigh Valley Medical Society, American College of Radiology (Fellow), Royal Society of Medicine of London (honorary), and a Fellow of the American College of Physicians since 1934.

Dr. Jackson was one of the leading roentgenologists of the State of Pennsylvania. He held the respect of a widespread circle of friends. His passing is a loss, not only to his family and his many friends, but to the medical profession in the section in which he resided.

EDWARD L. BORTZ, M.D., F.A.C.P.,
Governor for Eastern Pennsylvania.

DR. GEORGE CHARLES HENRY FRANKLIN

Dr. George Charles Henry Franklin, Lieutenant Colonel, Medical Corps, U. S. A., died suddenly following a heart attack April 23, 1939, at Fort Leavenworth, Kansas.

Colonel Franklin was born in California, November 5, 1886. He graduated in medicine at Cooper Medical College, May, 1912, after which he served for a year as intern and another year as resident physician in Mt. Zion Hospital, San Francisco, California. He entered the Medical Corps of the Army August 10, 1917 and was promoted through successive grades from First Lieutenant to that of Lieutenant Colonel on April 1, 1937. During the World War he was with the A.E.F. in France from May, 1918, to June, 1919.

This medical officer was an outstanding laboratory specialist. He was quiet, unassuming, earnest, sincere and a hard worker. He was assigned for the usual tour of an army officer of from two to four years to a number of important army stations. He served in Panama, 1928-31, as chief Bacteriologist of the Board of Health. After this he was given a year of detached service to attend the School of Tropical Medicine in London. On completion of the prescribed course he received the degree of D.T.M. and H. His next duty was that of instructor for a period of four years in Medical Entomology and Helminthology at the Army Medical School, Washington, D. C. His last assignment was chief of the laboratory service, Station Hospital, Fort Leavenworth, Kansas.

Colonel Franklin became an Associate of the American College of Physicians during 1936, and was advanced to Fellowship at the New Orleans Session, March 26, 1939.

JAMES C. MAGEE, Major General, U. S. Army,
The Surgeon General.

DR. MARY O'MALLEY

Dr. Mary O'Malley, nationally-known psychiatrist and neurologist and at one time the only woman clinical director for mental diseases in the United States, died January 30, 1939, at her home, 35 Brantford Place, Buffalo, N. Y. She had been ill for the last six months.

Prior to her retirement three years ago, Dr. O'Malley was in charge of more than 1,500 women patients at St. Elizabeth's Hospital, Washington, the largest institution for mental cases conducted by the federal government. She was the first woman physician accepted at St. Elizabeth's and held the position of clinical director for more than a quarter of a century.

Dr. O'Malley served as the head of many medical, neurological and pathological organizations and was president of the Medical Women's National Association in 1933. She contributed numerous scientific articles and in 1931 was a delegate to the International Medical Women's Association at Vienna and the International Neurological Congress at Berne.

Dr. O'Malley was born in Orleans County, daughter of Bridget Whalen O'Malley and Michael O'Malley, justice of the supreme court of New York State. Dr. O'Malley was educated in the vicinity schools and the University of Buffalo. She was graduated in medicine in 1897 and served her internship at the Sisters of Charity Hospital here.

Upon completing her internship, Dr. O'Malley was appointed woman physician at Binghamton State Hospital, where she remained for seven years until going to St. Elizabeth's Hospital where she made a brilliant record.

Dr. O'Malley is survived by her sisters, Anna and Margaret O'Malley of Buffalo, and one brother, John O'Malley of Barker. She became a Fellow of the American College of Physicians in 1928.

NELSON G. RUSSELL, M.D., F.A.C.P.,
Governor for Western New York.

DR. ALFRED FRIEDLANDER

A host of friends, as well as all of the doctors of Cincinnati, deeply mourn the recent passing of Dr. Alfred Friedlander, on May 28, 1939. His close association with the Medical College ever since his graduation from this school, his wide interests, his genial personality, and his wise counsel, placed him on the altar of medical fame. More recently his appointment as Dean of the University of Cincinnati Medical College again demonstrated his unusual ability in not only medical, but executive matters. Dr. Friedlander's background was one of fine preparation for the profession which he followed so successfully for many years. He received his B.A. degree from the Harvard University in 1892, and his M.D. degree in 1895 from the University of Cincinnati College of Medicine. He pursued for several years postgraduate study in pathology and medicine in the leading

universities of Germany and Austria. He served his internship at the Cincinnati General Hospital. His War record as Major in the Medical Corps, and Chief of the Medical Service, Post Hospital, Camp Sherman, was an enviable one.

At the time of his death, Dr. Friedlander was Professor of Medicine, University of Cincinnati College of Medicine, and Chief of Staff of the Chronic Disease Hospital. He was also Attending Physician at the Cincinnati General Hospital.

Dr. Friedlander was the author of a book on hypotension, contributed a chapter in Abt's "Pediatrics," and a chapter in Blumer's edition of Forcheimer's "Therapeusis of Internal Diseases." He was the author of many published articles.

Dr. Friedlander was a member of the American Pediatric Society; Ohio State Medical Association; Cincinnati Academy of Medicine, American Medical Association; and a Fellow of the American College of Physicians since 1931. In his passing the American College of Physicians loses one of its most valuable members.

JULIEN E. BENJAMIN, M.D., F.A.C.P.,
Cincinnati, Ohio.

DR. PAUL EUGENE LINEBACK

Dr. Paul Eugene Lineback, aged 59, died February 28, 1939, after a short illness. Dr. Lineback, a native of Winston-Salem, N. C., graduated from the Drake University College of Medicine, Des Moines, Iowa, in 1911. In 1912 and 1913 he served as Professor of Anatomy at Drake University College of Medicine, and in 1914 practiced at Anaconda, Montana. Later he did postgraduate work at Harvard University Medical School and was one of two southerners selected to contribute to the Carnegie Institute on anatomy. Dr. Lineback received an honorary lectureship at the University of London and also did postgraduate work at the Colonial Institute, Amsterdam, Holland. He was a member of the faculty of the University of Chicago from 1917 to 1922, later becoming associated with the Emory University School of Medicine as Professor of Microanatomy, which position he held at the time of his death. He was the author of a number of published articles, and co-author of "Anatomy of the Rhesus Monkey." He was a member of the American Association of Anatomists, Fellow, American Association for the Advancement of Science, and Fellow, American College of Physicians since 1927. Dr. Lineback was a superb teacher, a valuable leader in the medical school and a man of sterling personal character.

GLENVILLE GIDDINGS, M.D., F.A.C.P.,
Governor for Georgia.

DR. FRANK PARSONS NORBURY

Dr. Frank Parsons Norbury (F.A.C.P.), Jacksonville, Ill., died suddenly at his hospital for nervous and mental diseases at Jacksonville, March 14, 1939. A few years ago he developed Parkinson's disease, following an attack of poliomyelitis, from which he gradually became physically impaired, but had been able to attend patients at his institution during part of this time.

Dr. Norbury was born at Beardstown, Ill., August 5, 1863. After graduating from the Beardstown High School, he entered Illinois College, but before graduation transferred to the Medico-Chirurgical College of Philadelphia, 1886-87, and again transferred to the Long Island College of Medicine, from which he graduated with the degree of Doctor of Medicine in 1888; he later was honored with an A.M. degree from Illinois College in 1903.

Dr. Norbury formerly was Resident Physician, Pennsylvania Institution for Feeble Minded Children, 1888; Assistant Physician, Illinois Central Hospital, Jacksonville, 1888-93; Physician to Oak Lawn Retreat, 1896-1900; Superintendent and Medical Director, Norbury Sanatorium, Jacksonville, 1901-09; Superintendent Kankakee State Hospital, 1909-11; Alienist, Board of Administration of Illinois, 1911-13; Medical Director, Norbury Sanatorium, 1913 to time of his death; also at time of his death, Consulting Neuropsychiatrist, Wabash Employees' Hospital; Secretary, Section of Neurology and Medical Jurisprudence, 1893-94, and Member of the House of Delegates of the American Medical Association, 1904; Past President, Morgan County Medical Society; Member, American Psychiatric Association; Past President and Secretary, Mississippi Valley Medical Association; Professor of Internal Medicine, St. Louis College of Physicians and Surgeons, 1895-96; and Professor of Nervous and Mental Diseases, Keokuk (Iowa) Medical College, College of Physicians and Surgeons, 1904-08; Acting Medical Director of the National Committee for Mental Hygiene during the World War.

Dr. Norbury entered the practice of medicine at a time when there was limited clinical knowledge of the care and treatment of nervous and mental diseases. At the time he began his work in the State institutions, they were considered only a place of confinement where patients might be kept who were unable to be cared for in their homes. He advocated more careful study with case histories and more definite clinical diagnosis, that these cases might have proper treatment and be restored to their families.

At that time, there were no laboratory aids to diagnosis, so that clinical knowledge of the patient was obtained only by long hours of personal effort. When he began his administration, little was known of the modern knowledge and treatment of cases of paresis, which filled the greater percentage of beds in our State hospitals. He clearly saw these conditions and it was his pioneering efforts that have brought about the modern change in the institutions of the State.

As a Consultant, he was well known to the public and the medical profession of central Illinois for a quarter of a century. His personal and ethical relations with the medical profession have always been of the highest character, and for these attainments he will always be remembered by those who knew and loved him.

Dr. Norbury had been a Fellow of the American College of Physicians since 1917.

SAMUEL E. MUNSON, M.D., F.A.C.P.,
Governor for Southern Illinois.

DR. JOSEPH CARL KAMP

Dr. Joseph Carl Kamp, F.A.C.P., Casper, Wyoming, died on May 13, 1939, at the Scripps Metabolic Clinic, La Jolla, California, following an illness of several months' duration. He was 60 years of age.

Dr. Kamp was born on September 7, 1879, near Cologne, Germany, coming to America at an early age. His primary education was received in the Parochial and Public Schools and Saint Benedict's College of Newark, New Jersey, after which he entered the Medical Corps of the United States Army, serving through the Spanish-American War and later being stationed at Fort Riley, Kansas and Fort Douglas, Utah. He attended the University of Utah and then the Denver and Gross College of Medicine, later merged with the University of Colorado, receiving the degree of Doctor of Medicine in 1909.

The following year he entered the practice of medicine at Casper, Wyoming. Postgraduate medical study was received at the Chicago Polyclinic (1915), New York Postgraduate Medical School (1922, 1923, 1924, 1925, 1926, 1934), Santa Barbara College Hospital (1927), Mayo Clinic (1928), and the University of Vienna (1936). He became an Associate of the American College of Physicians in 1924 and was elected to Fellowship in 1929, being the first Wyoming physician to attain this distinction.

He was a member of the American Medical Association, the Wyoming State and Natrona County Medical Societies and a staff member of the Natrona County Memorial Hospital, and held a commission of Major in the Medical Reserve Corps of the United States Army.

Dr. J. C. Kamp was an outstanding individual. Prominent in his profession in the state of Wyoming and interested in civic and community problems in Casper, he will forever be cherished in memory by those who knew him.

GEORGE E. BAKER, F.A.C.P.

DR. JOHN ANDREW MURPHY

Dr. John Andrew Murphy died June 13, 1939 at his home 313 Dickinson Avenue, Swarthmore, Pennsylvania. Dr. Murphy was 59 years old.

Dr. Murphy was a graduate of the University of Pennsylvania School of Medicine, 1903; Assistant Professor of Clinical Immunology, University of Pennsylvania Graduate School of Medicine; Associate, Asthma Clinic, Presbyterian and Abington Memorial Hospitals and Germantown Dispensary and Hospital.

During the World War, he served in France for a year and a half, retiring from the army with the rank of lieutenant colonel. He was past commander of the Ainsworth Post, American Legion, Swarthmore.

Dr. Murphy was a member of the Philadelphia County Medical, the Association for Study of Allergy, and the Society for the Study of Asthma.

Dr. Murphy was elected an Associate of The American College of Physicians in 1925.

He is survived by his widow, Elizabeth; a son, Francis Blake Murphy, and a daughter, Mrs. Henry Hagert.

EDWARD L. BORTZ, M.D., F.A.C.P.

Governor for Eastern Pennsylvania.

ANNALS OF INTERNAL MEDICINE

VOLUME 13

AUGUST, 1939

NUMBER 2

NICOTINIC ACID IN NUTRITION *

By C. A. ELVEHJEM, *Madison, Wisconsin*

It is the goal of nutrition workers to make available as rapidly as possible all the knowledge necessary to handle the supply of foods and the demand for nutrients in such a way that nutritional deficiencies will be reduced to a minimum. However, there are many factors such as habit, economic conditions, ignorance, commercial manipulation of food supplies, etc., which militate against the attainment of this goal.

When nutritional deficiencies appear, the physician is expected to bring about rapid recovery even though the condition is the result of prolonged consumption of inadequate diets. It is apparent to most of us that the number of nutritional disorders is not decreasing. There are undoubtedly two reasons for this situation. First, more and more diseases are being associated with nutritional disturbances; and secondly, in spite of our increased knowledge of nutrition, the American diet is still far from ideal.

There is ample evidence that the knowledge necessary for the treatment of nutritional diseases has come from direct observations in the field and from experimental studies with laboratory animals. In fact many diseases were not conquered until the experimental animal entered the picture. There are, of course, exceptions, such as pernicious anemia, but this does not mean that greater progress might not have been enjoyed if it were possible to produce a similar disease in animals. During the past one and one-half years we have seen the fairly successful use of nicotinic acid in the treatment of pellagra and certain related disorders. I imagine my appearance on this program is dependent upon the fact that the discovery of the nutritional significance of nicotinic acid happened to be made in my laboratory. I do not mean to infer that we did not make a concerted effort to isolate the antipellagra factor, but I do want to emphasize that evidence for the significance of nicotinic acid in metabolism was accumulating in many laboratories.

* Given before the New Orleans meeting of the American College of Physicians, March 29, 1939.

Therefore, I do not propose to talk as an authority on pellagra or on the use of nicotinic acid in human nutrition. However, a survey of the work which led to the recognition of nicotinic acid may bring out certain helpful suggestions in the treatment of pellagra, as well as other nutritional diseases. Let us consider the status of pellagra and the antipellagra factor in 1930. The excellent work of Goldberger and coworkers had established pellagra as a deficiency disease. The protective factor was associated with the more heat stable fraction of the B complex which had been distinguished from vitamin B₁ by animal experimentation. A pellagra-like condition had been produced in rats on diets low in the B complex supplemented with an alcoholic extract of corn. Considerable difficulty was encountered in producing this condition consistently, but the growth stimulating effect of various foods when added to this diet continued to be used as a measure of antipellagra activity. In fact all the values in the literature were based on these assays except the limited figures reported by Sebrell¹ from studies with dogs. As late as 1932 Harris² made the following statement in a review on the water soluble vitamins. "The available evidence fairly well supports the assumption that the B₂ vitamin, as measured by the rat growth technic corresponds essentially with the pellagra-preventive factor for humans. Many aspects of the question, however, are still in the arena of controversy."

In 1930 the value of liver extract in the treatment of pellagra in man as well as its activity in the prevention of vitamin B₂ deficiency in rats was recognized. Goldberger and Sebrell³ found liver extract 343 to be a good source of the factor necessary for the prevention of black tongue in dogs. Spies⁴ and Smith and Ruffin⁵ found that fairly large amounts of liver extract by mouth were efficacious in treating pellagra. At about the same time I was working in the Biochemical Laboratory, Cambridge, England, and Dr. Guha, who was also working there, found that the liver extract, which I had brought along for another purpose, produced excellent growth in rats on a vitamin B₂ deficient diet. The following year Salmon and Guerrant⁶ found liver extract to be four times as rich in vitamin G (B₂) as a sample of brewer's yeast. We now know that the growth obtained in both cases must have been due mainly to the riboflavin present in the liver extract. However, the above results were sufficient to convince me that liver extract might be an excellent material for the isolation of the antipellagra factor.

Attempts in our laboratory to produce pellagra-like lesions in rats failed completely, and we turned our attention to chicks. A pellagra-like condition was produced in the chick by feeding a heated natural grain ration, and the assays of our fractions from liver extract depended upon the prevention of these lesions. We⁷ soon had the first indication that the factor active in this syndrome was separate from riboflavin which Kuhn, György, and Wagner-Jauregg⁸ had just isolated and shown to have growth-promoting properties in rats. Concentrates of flavin were completely inactive for the chick whereas purified fractions from liver retained their potency after complete removal of riboflavin. Lepkovsky and Jukes⁹ soon confirmed our

experimental results and introduced the name "filtrate factor" for the active substance in the filtrate after removal of the flavin with fuller's earth. This designation did not exactly please us since naturally we felt that we were dealing with the antipellagra factor, and Dr. Lepkovsky and I had many friendly arguments over the question. We both recognized that there was no evidence available to show that the pellagra-like condition in chicks was identical with human pellagra. It was therefore necessary for us to repeat our work using dogs, since most authorities agreed that black tongue in dogs is identical with human pellagra. Again¹⁰ flavin had no effect on black tongue whereas the purified concentrates free of flavin were highly active in curing black tongue. Birch, György and Harris¹¹ soon confirmed the fact that flavin had no curative action in dogs, and Dann,¹² Spies,¹³ and Fouts, Lepkovsky, Helmer, and Jukes¹⁴ reported complete inactivity of flavin in the treatment of human pellagra.

Further purification of the liver fractions gave concentrates which contained very small amounts of solid material and which were highly active in both chicks and dogs. We were inclined to believe that the chick and dog required the same factor. Within a very short period we¹⁵ demonstrated the activity of nicotinic acid in the cure of black tongue, and isolated nicotinic acid amide from the liver extract concentrates. When we¹⁶ tried nicotinic acid or the amide on the chicks they were completely inactive. Thus the chicks had provided an excellent means of assay, not because we were actually testing for nicotinic acid, but because we were testing for the chick antidermatitis factor which followed nicotinic acid amide very closely.

I hope I have not bored you with these details, but they demonstrate the importance of using different species when studying human nutrition. I do not mean to infer that the fundamental metabolism in different species varies greatly, but it is evident that we may be more successful in producing certain deficiencies in one animal and other deficiencies in another species. Thus the rat was used successfully in separating the antipellagra factor from vitamin B₁, the chick for separating it from riboflavin, and the dog for establishing its relation to nicotinic acid and not to the chick antidermatitis factor. In fact at the present time no one has been able to demonstrate that either the rat or the chick needs nicotinic acid preformed in the diet—yet cozymase, which contains nicotinic acid, is present in both rats and chicks.

Returning to the rat, this animal has been valuable in demonstrating the existence of at least two additional factors in the B complex; namely, vitamin B₆ and factor W. In the absence of vitamin B₆ the rat develops acrodynia, which is undoubtedly the same condition which was called pellagra in the earlier work. Birch, György, and Harris¹¹ in 1935 demonstrated conclusively that vitamin B₆ was distinct from the antipellagra factor. They found corn and molasses, foods known to be deficient in the P-P factor, to be good sources of vitamin B₆ and liver extract, which was rich in the P-P factor, to be low in vitamin B₆. Today if we give nicotinic acid to rats suffering from vitamin B₆ deficiency, there is no improvement whatsoever.

Very recently Helmer, Fouts, Lepkovsky, and Jukes have produced a hypochromic anemia in dogs on a vitamin B₆ low diet and have cured the condition with crystalline vitamin B₆.

If rats are placed on a purified diet devoid of all the B vitamins, and if thiamine, riboflavin, nicotinic acid, vitamin B₆, and chick antidermatitis factor are supplied in adequate amounts, the rats fail to grow until another factor which we¹⁷ have designated as factor W is added. We have recently obtained similar results with dogs. Factor W is present in the so-called filtrate from liver extract in addition to nicotinic acid and chick antidermatitis factor. Thus we have six separate and distinct B vitamins, and if I had time I could give you preliminary evidence for several more.

What does this mean in practical nutrition? Some of you may think that we are having a contest to see how many separate factors can be found. We will enjoy real success in the treatment of nutritional deficiencies only when all these factors are recognized. The real value of this knowledge will not depend so much on the use of the individual chemical entities, although this may be important in many cases, but rather on the interrelationship of each of these factors. Thus diets low in nicotinic acid or compounds which yield nicotinic acid on ingestion allow the development of pellagra, but such diets may also be low in other related vitamins. A diet deficient in only one nutritional factor but complete in all others is the ideal experimental diet which nutritional workers are continually looking for—but such rations are rarely obtained. Even those based on the original Goldberger diet contain some nicotinic acid and may be low in thiamine and riboflavin. The great value of the Goldberger diet is that black tongue develops before the other deficiencies are encountered, but now that we can add pure nicotinic acid, it is possible to demonstrate some of the other limitations. The supplementary value of thiamine and riboflavin in the treatment of pellagra has already been reported. Sebrell and Butler¹⁸ have recently reported the development of riboflavin deficiency in patients maintained on the Goldberger diet. There may be other factors which are supplied in a limiting amount. Langston, Darby, Shukers, and Day¹⁹ have obtained a nutritional cytopenia in monkeys maintained on the Goldberger ration. This syndrome was not cured by thiamine, riboflavin, or nicotinic acid, but liver extract contained the active factor. The Goldberger diet contains 65 to 75 per cent of corn. If this corn is replaced by sucrose and the required amounts of nicotinic acid, thiamine and riboflavin added, the dogs will grow for only a week or two and then begin to lose weight. The addition of 2 per cent liver extract renders the diet complete. Thus a small amount of liver extract supplies the same factors as 70 per cent of corn. Vitamin B₆ and factor W are at least two of the factors concerned here. Thus the results obtained with nicotinic acid may depend upon the actual amount of corn consumed by the patient.

It is evident therefore that there is danger in the wholesale treatment of pellagrins on severely deficient diets with pure nicotinic acid or purified

concentrates of nicotinic acid. What approach are we to make? First let me point out that foods carrying only fair amounts of nicotinic acid may be useless in treating severe pellagra regardless of the other factors they carry. Nicotinic acid is the critical deficiency and it must be provided before any response can be obtained. The great difficulties encountered in treating pellagra before nicotinic acid was available substantiate this conclusion. Similar evidence is available from our dog work. You will remember that Sebrell assayed foods for the P-P factor by determining what level of food would protect the dog from black tongue over a considerable period of time. We started with young dogs, produced black tongue, and cured the symptoms with concentrates and finally nicotinic acid. The response was very rapid. During the past year we have been assaying foods in the same way. When wheat germ, powdered milk, or dried grass is given in one dose, no improvement is obtained. The animal is unable to digest the food sufficiently to liberate the nicotinic acid present. Foods that are richer and can be fed in smaller quantities, such as liver, kidney, lean meat and yeast, work considerably better.

The rapid assimilation of nicotinic acid, even in the presence of severe intestinal disturbances, undoubtedly explains the success with which it has been used in the field. At present there appears to be no compound which is more useful. We²⁰ have tested a number of pyridine derivatives on dogs, and although nicotinamide, ethyl nicotinate, nicotinic acid N methyl amide, nicotinic acid N diethyl amide (coramin), and nicotinuric acid are active, none of these compounds seem to have any virtue over nicotinic acid. Trigonellin, pyridine, quinolinic acid, picolinic acid, isonicotinic acid, nipe-cotic acid; β -amino pyridine and related compounds are all inactive.

As long as severe pellagra is encountered, I imagine the use of nicotinic acid will have to be continued, but when it is used, we must remember that there are at least five other members of the B complex which may also be low. Fortunately both thiamine and riboflavin are available in synthetic form, and we are hopeful that some of the others may be available within a reasonable length of time. However, the supply of most of these factors through foods will be considerably cheaper for some time.

I cannot go into the great variations in the amount of nicotinic acid required for the treatment of pellagra in different patients. This has been discussed by Spies, Sydenstricker, and others. Several workers have observed considerable variation in the response made by different dogs to nicotinic acid. We have preliminary evidence that a more rapid response is obtained after feeding a factor W concentrate for a short time before giving nicotinic acid. Much more work is necessary, but these relationships are not surprising since at least four of the vitamins which I have discussed are related to the respiratory enzyme systems. Thiamine is related to cocarboxylase, which is necessary for the normal metabolism of pyruvic acid. Riboflavin is a component of flavoproteins, which act as hydrogen carriers, and probably also a component of the prosthetic group in other enzymes,

such as xanthine oxidase. Nicotinic acid is a component of both cozymase and cozymase II, both of which are coenzymes for a large number of oxidation mechanisms. We have recently shown that tissues taken from animals suffering from a factor W deficiency have a reduced rate of oxygen uptake.

I might mention our studies on the changes in the cozymase content of tissues during nicotinic acid deficiency. We used the Euler-Myrbäck method for estimating the cozymase content. Using both dogs and pigs we were unable to demonstrate any change in the blood, but very significant decreases were obtained in the liver and muscle during nicotinic acid deficiency.

Returning to the nutritional significance of nicotinic acid, I want to emphasize that the incidence of pellagra in certain areas of this country and other parts of the world is a temporary condition brought about by environmental conditions. Nicotinic acid as such is an emergency measure. Our goal should be the modification of the diet so that the people in these areas would obtain sufficient nicotinic acid, as well as the other essentials, from foods. This does not mean that certain foods could not be fortified with nicotinic acid, when experimental work has shown the proper means of fortification. In any case, the great need is further knowledge of the distribution of these factors in foods. I know it is a long and tedious job and one which is not very fascinating, but it must be done, and I hope that you as physicians will lend your support to such studies. I believe that this country is still sufficiently agricultural to produce the foods adequate for a normal diet, so that we may consume pleasing foods rather than obtaining our vitamins from the drug store except in emergencies.

BIBLIOGRAPHY

1. SEBRELL, W. H.: Table showing the pellagra-preventive values of various foods, Pub. Health Rep., 1934, xlix, 754-756.
2. HARRIS, L. J.: Vitamins, *Ann. Rev. Biochem.*, 1932, i, 337-412.
3. GOLDBERGER, J., and SEBRELL, W. H.: The blacktongue preventive value of Minot's liver extract, Pub. Health Rep., 1930, xlv, 3064-3070.
4. SPIES, T. D.: Pellagra: Improvement while taking so-called "pellagra-producing" diet, *Am. Jr. Med. Sci.*, 1932, clxxxiv, 837-845.
5. SMITH, D. T., and RUFFIN, J. M.: Treatment of pellagra with liver extracts, *Jr. Clin. Invest.*, 1933, xii, 963.
6. SALMON, W. D., and GUERRANT, N. B.: Liver extract as a source of vitamins B and G, *Science*, 1931, lxxiii, 243-244.
7. ELVEHJEM, C. A., and KOEHN, C. J., JR.: Studies on vitamin B₂ (G). The non-identity of vitamin B₂ and flavins, *Jr. Biol. Chem.*, 1935, xviii, 709-728.
8. KUHN, R., GYÖRGY, P., and WAGNER-JAUREGG, T.: Über eine neue Klasse von Naturfarbstoffen, *Ber. Chem. Ges.*, 1933, lxxvi, 317-320; Über die aus Eiklar und Milch isolierten Flavine, *ibid.*, 1577-1582.
9. LEPKOVSKY, S., and JUKES, T. J.: The vitamin G requirement of the chick, *Jr. Biol. Chem.*, 1935, cxi, 119-131.
10. KOEHN, C. J., JR., and ELVEHJEM, C. A.: Studies on vitamin G (B₂) and its relation to canine blacktongue, *Jr. Nutrition*, 1936, xi, 67-76.

11. BIRCH, T. W., GYÖRGY, P., and HARRIS, L. J.: The vitamin B₂ complex. Differentiation of the antiblacktongue and the "P.-P." factors from lactoflavin and vitamin B₆ (so-called "Rat-Pellagra" factor) Parts 1-6, *Biochem. Jr.*, 1935, xxix, 2830-2850.
12. DANN, W. J.: The vitamin G complex. I. The nonidentity of rat dermatitis due to vitamin B₆ deficiency and the dermatitis of human pellagra, *Jr. Nutrition*, 1936, xi, 451-462.
13. SPIES, T. D.: Personal communication.
14. FOUTS, P. J., LEPKOVSKY, S., HELMER, O. M., and JUKES, T. H.: Successful treatment of human pellagra with the "Filtrate Factor," *Proc. Soc. Exper. Biol. and Med.*, 1936, xxxv, 245-247.
15. ELVEHJEM, C. A., MADDEN, R. J., STRONG, F. M., and WOOLLEY, D. W.: The isolation and identification of the anti-black tongue factor, *Jr. Biol. Chem.*, 1938, cxxiii, 137-149.
16. MICKELSEN, O., WAISMAN, H. A., and ELVEHJEM, C. A.: The inactivity of nicotinic acid in chick dermatitis, *Jr. Biol. Chem.*, 1938, cxxiv, 313-320.
17. ELVEHJEM, C. A., KOEHN, C. J., JR., and OLESON, J. J.: A new essential dietary factor, *Jr. Biol. Chem.*, 1936, cxv, 707-719.
18. SEBRELL, W. H., and BUTLER, R. E.: Riboflavin deficiency in man, *Pub. Health Rep.*, 1938, liii, 2282-2284.
19. LANGSTON, W. C., DARBY, W. J., SHUKERS, C. F., and DAY, P. L.: Nutritional cytopenia (vitamin M deficiency) in the monkey, *Jr. Exper. Med.*, 1938, lxviii, 923-940.
20. WOOLLEY, D. W., STRONG, F. M., MADDEN, R. J., and ELVEHJEM, C. A.: Anti-black tongue activity of various pyridine derivatives, *Jr. Biol. Chem.*, 1938, cxxiv, 715-723.

OBSERVATIONS UPON THE EXPERIMENTAL USE OF SULFAPYRIDINE. I. THE RELATION OF STRAIN RESISTANCE TO THE CHEMOTHERAPEUTIC EFFECTS OF SULFAPYRIDINE IN EXPERIMENTAL PNEUMOCOCCAL INFECTIONS IN MICE *

By PERRIN H. LONG, M.D., and ELEANOR A. BLISS, Sc.D.,
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IN the *Lancet* of May 28, 1938, L. E. H. Whitby¹ reported that 2 (p-aminobenzenesulphonamido) pyridine (sulfapyridine) was "chemotherapeutically active in experimental infections in mice against pneumococci of types I, II, III, V, VII, VIII and especially against types I, VII and VIII." Whitby also stated in this paper that the drug appeared "to exert a definite action on the capsule of the pneumococcus." Within a very short time after this communication appeared, Evans and Gaisford² reported that they had treated with sulfapyridine 100 patients suffering from lobar pneumonia, and that in this group of patients the case fatality rate was 8 per cent; this was to be compared with a fatality rate of 27 per cent in a group of 100 patients who had received symptomatic treatment for lobar pneumonia. These important observations naturally created a great deal of interest throughout the world. It was not very long before general confirmation of Whitby's observations began to appear³⁻⁹ and, while the results of certain investigators were at partial variance with those reported by Whitby, there can be little doubt that sulfapyridine is a fairly satisfactory agent for the treatment of experimental pneumococcal infections in mice. In this communication we will record certain of our observations upon the use of sulfapyridine in pneumococcal experimental infections.

During the past year we have conducted extensive experiments upon the chemotherapeutic properties of sulfapyridine in experimental pneumococcal infections in mice. The results of these observations are recorded in table 1. We soon noted that while sulfapyridine produced more satisfactory results in the treatment of pneumococcal infections in mice than we had obtained previously with any other chemical compound, nevertheless, we could not approach those reported by Whitby. This was especially true insofar as our results in the treatment of type I pneumococcal infections were concerned.

A review of our methods of inoculation and of our systems of dosage showed no great divergence from those used by Whitby.¹ We were at first

* Received for publication July 1, 1939.

This investigation was supported by a grant from The Chemical Foundation, Inc., of New York City.

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TABLE I
Sulfapyridine Therapy in Experimental Pneumococcal Peritonitis in Mice

No. Mice	Organism	Inoculum M.L.D.	Type of Treatment	Deaths—Days after Infection											Survivals	
				1	2	3	4	5	6	7	8	9	10	11-30	No.	%
130	Pneu. I	950	D 10		15	47	39	15	1	2				1	10	7.7
40	Pneu. I	575	F 10		2	14	17	4						1	1	2.5
35	Pneu. I	805	G 20		23	11	1								0	0
20	Pneu. I	500	H 30		4	14	1	1							0	0
190	Pneu. I	775	Controls	188	2										0	0
50	Pneu. II	890	D 10		7	13	10	5	7	6	1	1			0	0
30	Pneu. II	890	Controls	30											0	0
50	Pneu. III	1040	D 10	1	4	6	8	2	1	25	2	1			0	0
30	Pneu. III	1040	Controls	30											0	0

D 10 = 10 mg. *per os* T.I.D. for 5 days, B.I.D. for 1 day, Q.D. for 1 day.
 F 10 = 10 mg. *per os* 4 I.D. for 4 days, T.I.D. for 2 days, B.I.D. for 1 day.
 G 20 = 20 mg. *per os* at 4 and 12 hours after infection, then Q.D. for 4 days.
 H 30 = 30 mg. *per os* immediately after infection and 6 hours later, then Q.D. for 3 days.

inclined to attribute our less favorable results to a greater "virulence" of our strains of pneumococci for the mouse. However, after MacLean, Rogers and Fleming¹⁰ reported that, upon the basis of their in vitro studies, they had reached the conclusion that pneumococci might vary markedly in their sensitivity to the drug and had apparently confirmed this by in vivo treatment tests, we began to wonder whether our highly "virulent" strain might not also be relatively insensitive to the chemotherapeutic effects of sulfapyridine.

We³ had tested previously the bacteriostatic effects of sulfanilamide and sulfapyridine upon the growth of our type I strain of pneumococcus in beef infusion, neo-peptone dextrose broth, and had found the strain to be moderately sensitive to sultanilamide and quite sensitive to sulfapyridine. Retests of the bacteriostatic activity of these two compounds are shown in table 2. It is to be noted that under the conditions of the test, sulfapyridine was a highly effective bacteriostatic agent.

TABLE II

The Bacteriostatic Effects of Sulfapyridine and Sulfanilamide upon the Growth of Five Strains of Type I Pneumococci in Beef Infusion, Neo-Peptide Dextrose Broth Cultures

Organism	Inoculum orgs./c.c.	Growth—Colonies/1 c.c. in 18 hours		
		Control	Sulfanilamide 10 mg. %	Sulfapyridine 10 mg. %
I	600	150 mil.	1,120,000	100
	400	80 mil.	3,400	10
	1,450	100 mil.	141,000	2,000
S V-I	760	160 mil.	147,000	2,140
	22,000	130 mil.	46,000	330
	1,180	70 mil.	15,000	11,000
S V-I/P/47	1,180	90 mil.	32 mil.	480,000
	56,000	140 mil.	190 mil.	25 mil.
	1,400	100 mil.	110 mil.	147,000
	19,200	720 mil.	380 mil.	5 mil.
	720	510 mil.	300 mil.	125,000
	840	190 mil.	350 mil.	590,000
Neufeld I	480	240 mil.	35,000	500
	220	210 mil.	330	10
	2,400	160 mil.	12,000	19,000
Neufeld I	860	430 mil.	10,000	2,100
	660	290 mil.	7,000	1,060
	2,200	220 mil.	2,000	3,000

I = Highly mouse-virulent, in vivo sulfapyridine resistant strain.

S V-I = Highly mouse-virulent, in vivo sulfapyridine susceptible strain obtained from Dr. Colin MacLeod.

S V-I/P/47 = Highly mouse-virulent, in vivo sulfapyridine resistant strain obtained from Dr. Colin MacLeod.

Neufeld I = Originally came from the New York State Board of Health Laboratories.

Neufeld I = Originally came from the New York City Board of Health Laboratories.

TABLE III
The Comparative Therapeutic Effects of Sulfapyridine in Experimental Pneumococcal Infections in Mice Produced by "Resistant" and "Susceptible" Strains of Type I Pneumococci

No. Mice	Organism	Inoculum M.L.D.	Type of Treatment	Deaths—Days after Infection											Survivals	
				1	2	3	4	5	6	7	8	9	10	11-30	No.	%
20	Pneu. I	500	H 30		4	14	1	1							0	0
10	Pneu. I	500	Controls	10											0	0
20	Pneu. I (SV/1)	620	H 30	1		1			1						17	85
10	Pneu. I (SV/1)	620	Controls		10											
20	Pneu. I (SV/P47)	560	H 30	1	10	7			2						0	0
10	Pneu. I (SV/P47)	560	Controls		10											

H 30 = 30 mg. *per os* immediately after infection and 6 hours later, then Q.D. for 3 days.

At this point Dr. Colin MacLeod informed us that he had developed a "sulfapyridine-fast" mutant from a strain of type I pneumococcus, the original strain having been very susceptible to the chemotherapeutic effects of sulfapyridine. He very kindly sent us the parent strain S V-I and the "sulfapyridine-fast" strain S V-I/P/47, the properties of which he has recently described.^{11, 12}

These strains, together with Neufeld type I strains from two different sources, were tested by our technic to determine their sensitivity to the bacteriostatic effects of sulfanilamide and sulfapyridine *in vitro*. As will be noted in table 2, the parent strain S V-I and the two Neufeld strains were as susceptible to the bacteriostatic effects of sulfapyridine as was our own type I pneumococcus. The "sulfapyridine-fast" organism S V-I/P/47 was, on the contrary, quite insensitive to the bacteriostatic effects of sulfanilamide and was only moderately sensitive to the effects of sulfapyridine. MacLeod¹¹ has shown that experimental infections in mice produced by the S V-I strain yield readily to treatment with sulfapyridine, and that the converse is true with infections produced by strain S V-I/P/47. We, therefore, tested the comparative therapeutic effects of sulfapyridine in infections produced in mice by inoculation of our type I strain of pneumococcus, S V-I and S V-I/P/47. The results of these therapeutic attempts are recorded in table 3.

As was to be expected from our previous experience, no mice infected with our strain of type I pneumococcus survived. The same was true of the mice infected with the "sulfapyridine-fast" strain S V-I/P/47, while 17 of the mice infected with strain S V-I survived. It is interesting to note at this point that the control mice infected with strains S V-I and S V-I/P/47 died on the second day of their infection, while the other control mice died within 22 hours after they were inoculated.

DISCUSSION

These experiments confirm the observation, as has already been pointed out, that strain differences in the susceptibility of pneumococci to sulfapyridine do exist. Furthermore, they reveal the fact that strains of pneumococci which appear to be highly susceptible to the *in vitro* bacteriostatic effects of sulfapyridine may produce infections *in vivo* which differ markedly in their response to the chemotherapeutic action of the drug. They also serve to emphasize again the possibility that naturally resistant strains exist and that the mechanism of this resistance to the chemotherapeutic effects of sulfapyridine *in vivo* may be quite different from that of a normally susceptible strain. Certainly, the variations in the response of the organisms to the *in vitro* bacteriostatic effects of sulfapyridine suggest that this might be true. The practical significance of these observations lies in the fact that it has been shown that marked strain differences in susceptibility do occur and, hence, it would be wise to take advantage of this fact in

assessing the activities of new chemical compounds. They also suggest that variations in the susceptibility of pneumococci to sulfapyridine will be of importance in the therapy of pneumococcal pneumonia in man with the drug.

CONCLUSION

Marked differences exist among strains of pneumococci in their response to the chemotherapeutic effects of sulfapyridine.

We are indebted to the Calco Chemical Company, Inc., and to Merck and Company, Inc., for the sulfapyridine used in these experiments.

BIBLIOGRAPHY

1. WHITBY, L. E. H.: Chemotherapy of pneumococcal infections with 2(p-aminobenzene-sulphonamido) pyridine, *Lancet*, 1938, i, 1210.
2. EVANS, G. M., and GAISFORD, W. F.: Treatment of pneumonia with 2 (p-aminobenzene-sulphonamido) pyridine, *Lancet*, 1938, ii, 14.
3. LONG, P. H., BLISS, E. A., and FEINSTONE, W. H.: The effects of sulfapyridine, sulfanilamide and related compounds in bacterial infections, *Penn. Med. Jr.*, 1939, xlii, 483.
4. COOPER, F. B., GROSS, P., and LEWIS, M.: Chemotherapeutic evaluation of sulfanilamide and 2 (sulfanilamide) -pyridine in Type II pneumococcal infections in mice and rats, *Proc. Soc. Exper. Biol. and Med.*, 1939, xl, 37.
5. HILLES, C., and SCHMIDT, L. H.: Sulfanilamidepyridine (2 para-aminobenzenesulfonamidopyridine) in experimental infections with Type XXII pneumococcus, *Proc. Soc. Exper. Biol. and Med.*, 1939, xl, 37.
6. RAIZISS, G. W., SEVERAC, M., MOETSCH, J. C., and CLEMENCE, L. W.: Comparative effects of sulfapyridine and sulfanilamide in Type II pneumococcal infections of mice, *Proc. Soc. Exper. Biol. and Med.*, 1939, xl, 434.
7. SCHMIDT, L. H., and HILLES, C.: Further studies on therapeutic properties of sulfapyridine in experimental pneumococcus infections, *Proc. Soc. Exper. Biol. and Med.*, 1939, xl, 611.
8. BLISS, E. A., FEINSTONE, W. H., GARRETT, A. W., and LONG, P. H.: Sulfapyridine and sulfanilamide in experimental pneumococcal, meningococcal, Welch bacillary and Friedländer's bacillary infections in mice, *Proc. Soc. Exper. Biol. and Med.*, 1939, xl, 619.
9. GREEY, P. H., MACLAREN, D. B., and LUCAS, C. C.: Comparative chemotherapy in experimental pneumococcal infections, *Canad. Med. Jr.*, 1939, xl, 319.
10. MACLEAN, I. H., ROGERS, K. B., and FLEMING, A.: M. & B. 693 and pneumococci, *Lancet*, 1939, i, 562.
11. MACLEOD, C. M., and DADDI, G.: A "sulfapyridine-fast" strain of pneumococcus Type I, *Proc. Soc. Exper. Biol. and Med.*, 1939, xli, 69.
12. MACLEOD, C. M.: Metabolism of "sulfapyridine-fast" and parent strains of pneumococcus Type I, *Proc. Soc. Exper. Biol. and Med.*, 1939, xli, 215.

EPIDEMIC SYPHILIS, ITS RECOGNITION AND MANAGEMENT BY THE PHYSICIAN *

By E. GURNEY CLARK, M.D., *Nashville, Tennessee*

INTRODUCTION

SYPHILIS exhibits many of the characteristics of epidemic disease. It has the capacity of producing a sharp increase in incidence in a short time.¹ It often gives rise to localized outbreaks; and, in at least one historic instance, it appeared as a sudden outbreak over a wide area. This concept with regard to syphilis is not a new one. More than 100 reports of localized epidemics of syphilis can be found in the literature under titles which imply epidemicity.

The mild character or total absence of the early manifestations; the "conspiracy of silence" with regard to the disease; and the almost universal failure to recognize its epidemic nature are the factors that prevent its ultimate eradication or control. The recognition and management of epidemic syphilis are obligations of the medical profession.

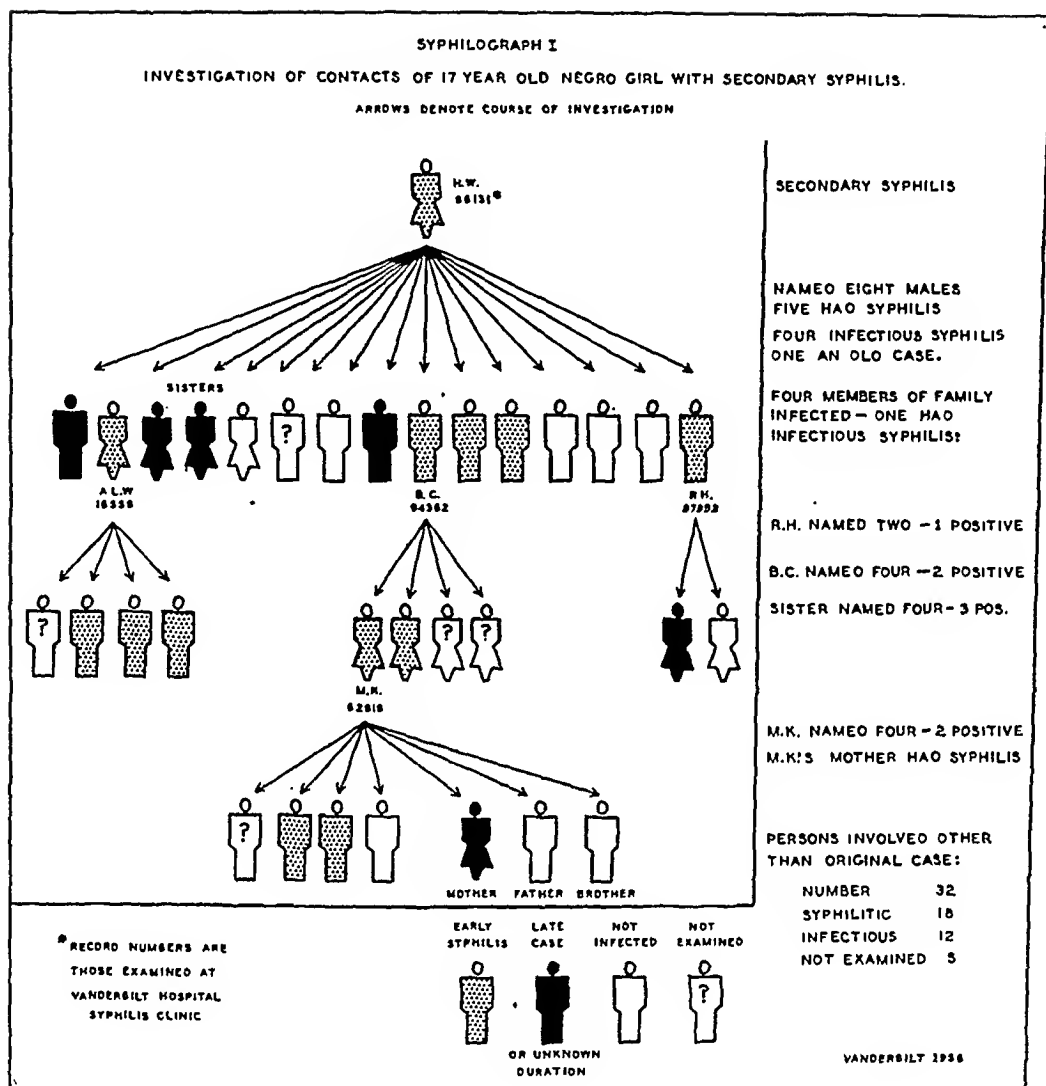
EPIDEMICS OF SYPHILIS

The following epidemics were discovered and brought under control in the routine management of patients in the syphilis clinic of the Vanderbilt University Hospital.

A young negro girl, H. W. (syphilograph 1), came to the clinic because of early syphilis of the skin and mucous membranes. When she learned that the lesions were due to syphilis and were highly infectious and that she had doubtless exposed others to the disease she disclosed the names of eight young men with whom she had had sexual intercourse and promised to assist in persuading them to have an examination. All of these and six members of her family were examined either by their own physicians or in the syphilis clinic of the Vanderbilt University Hospital. Of these 14 persons, nine were found to have syphilis, five of whom were in an infectious stage. A sister, A. L. W., was totally unaware of her infectious lesions and because of this it was a simple matter to develop in her a sympathy for her contacts who might have no knowledge of lesions. She designated four sexual contacts, three of whom were found by their own physicians to have infectious or potentially infectious syphilis. If these physicians investigated the contacts of these young boys it was not brought to our attention. B. C. and R. H., two of the sexual contacts of the original case, were examined by us and found to have secondary syphilis. Two others were also infectious. Three of the contacts were not infected. One was found to have inadequately treated syphilis of several years' duration. This patient was induced to return to his physician for continuance of his treatment. Subsequent examination of other contacts related to this epidemic disclosed four additional cases of early syphilis and

* Read at the New Orleans meeting of the American College of Physicians, March 29, 1939.

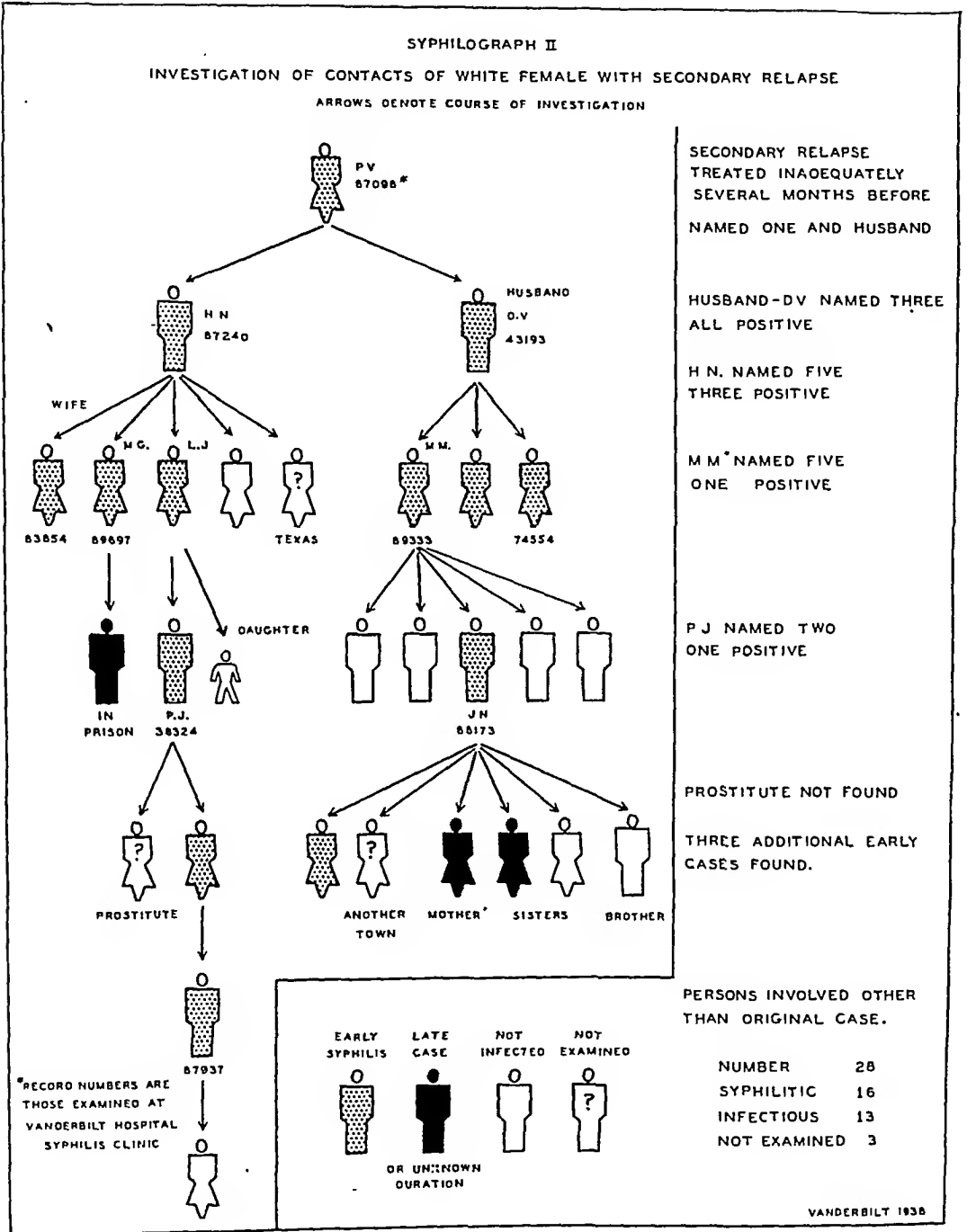
From the Department of Medicine, Vanderbilt University School of Medicine.
The epidemiological investigations were made possible through funds granted by the United States Public Health Service.



was instrumental in returning two old cases to treatment. In this epidemic 18 cases of syphilis were found among 32 persons designated as contacts. Several were totally unaware of the fact that they had syphilis or that they had been exposed to it.

A married white woman, P. V. (syphilograph 2), sought treatment because of a recurrence of a generalized rash six months after inadequate treatment for syphilis. A frank discussion convinced her of the danger of lapsing treatment and induced her to name one extra-marital contact. Her husband, also exhibiting secondary lesions, disclosed three of his contacts, all of whom were found to have infectious syphilis. One of these, M. M., brought to the clinic one of her contacts, J. H., who had primary syphilis, and named three others who were found not to be infected. H. N., the designated extra-marital contact of P. V., disclosed five names and three of the girls had early syphilis. Three additional cases were disclosed. Sixteen of the 26 persons involved were found to have syphilis. There were 13 of these who were infectious or potentially infectious.

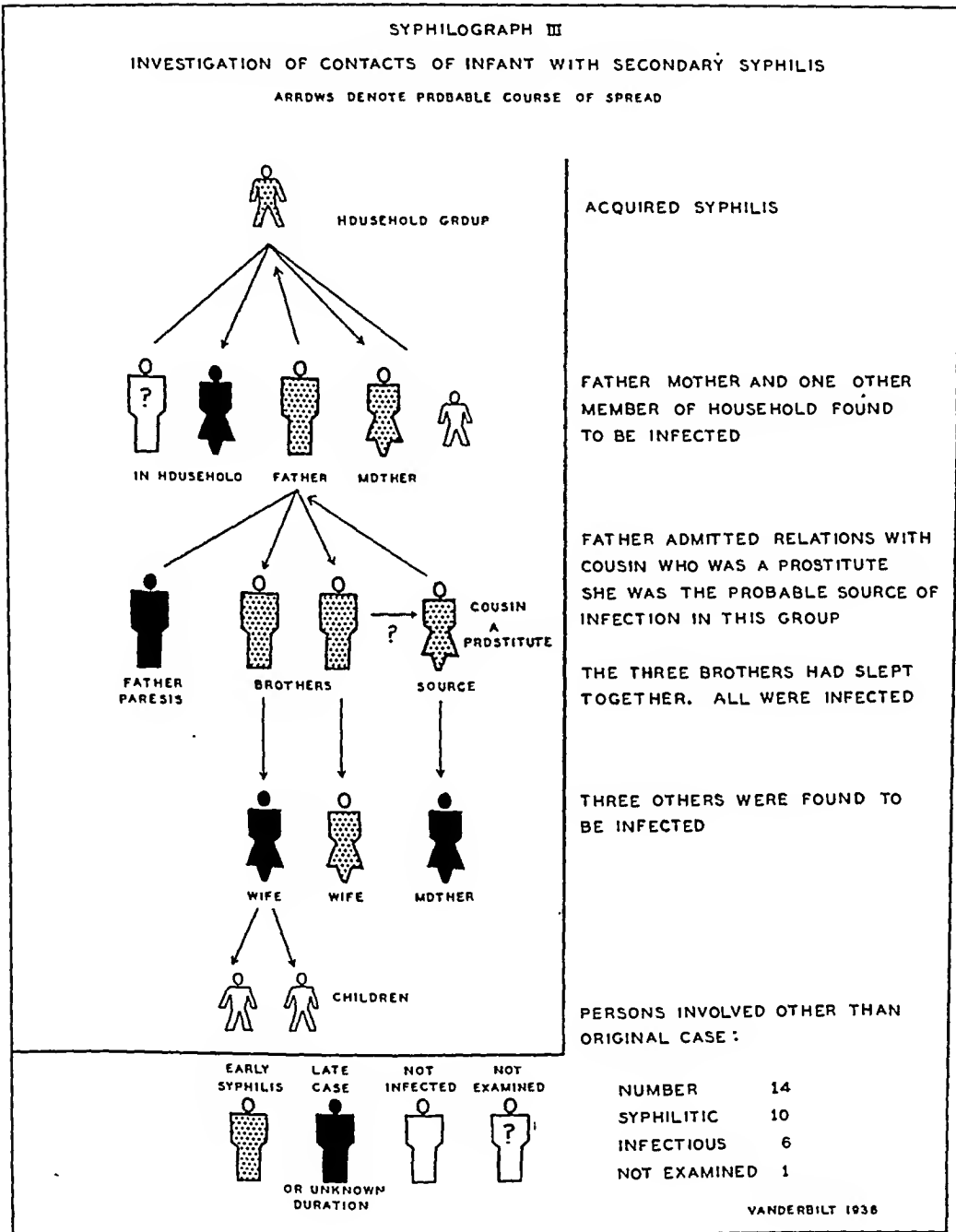
An epidemic of syphilis in a family is shown in syphilograph 3. Acquired syphilis was diagnosed in an infant seen in the pediatric clinic of the Vanderbilt University Hospital. The father, mother, two uncles and their wives, a cousin, a grandfather



and another member of the household were found to have the disease. The source of the infection was thought to be a cousin who is a prostitute.

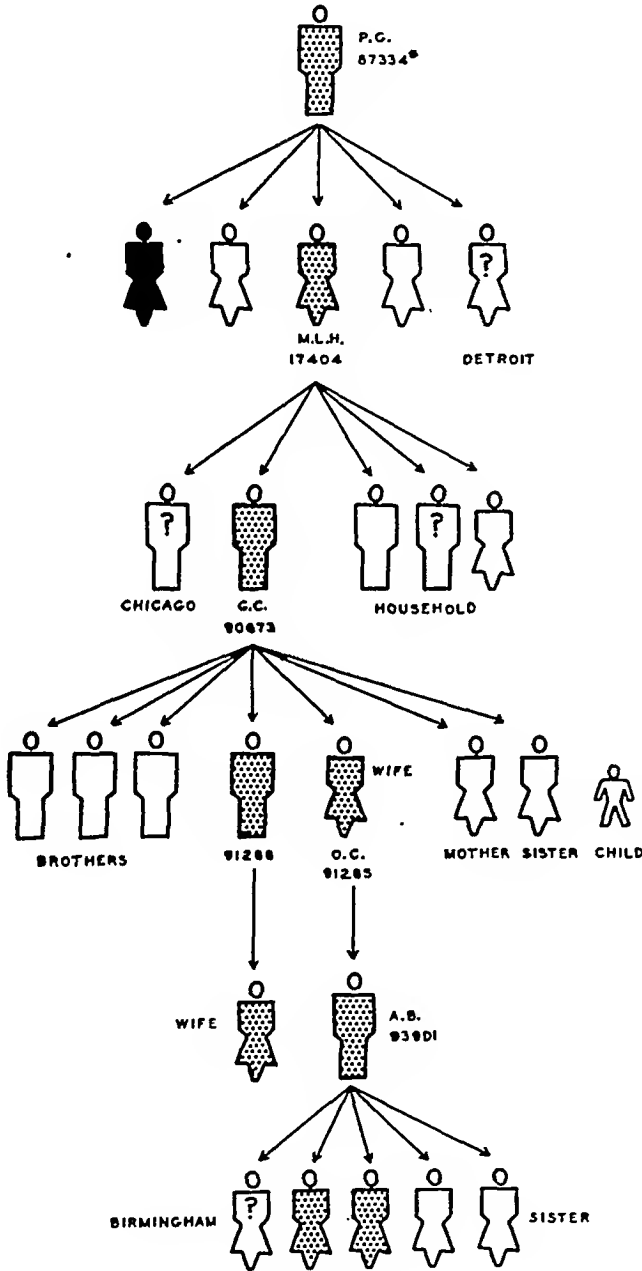
P. G., a young negro boy (syphilograph 4), was convinced by us that his name would not be divulged and gave information that led to the discovery of nine additional cases of syphilis.

These studies indicate that every case of syphilis is part of a localized outbreak; that the patient who comes to the physician can and often will



disclose facts which lead to the detection of this local epidemic. From this starting point the physician is able to discover and bring under control a large number of highly infectious individuals. The above four patients who sought treatment for acute syphilis were used as starting points and 39 additional infectious cases were disclosed.

SYPHILOGRAPH IV
INVESTIGATION OF CONTACTS OF YOUNG NEGRO WITH SECONDARY SYPHILIS
ARROWS DENOTE COURSE OF INVESTIGATION



P.G. GAVE FIVE NAMES
ONE EARLY CASE FOUND
LED TO ANOTHER

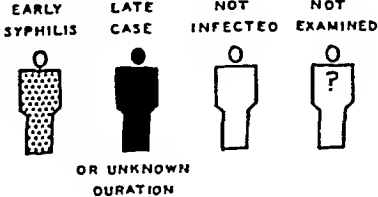
G.C. INFECTED HIS WIFE O.C.
SHE GAVE ONE NAME
HE WAS INFECTED

A.B. NAMED FOUR
TWO WERE INFECTED

PERSONS INVOLVED OTHER
THAN ORIGINAL CASE

NUMBER	25
SYPHILITIC	9
INFECTIOUS	8
NOT EXAMINED	4

*RECORD NUMBERS ARE
THOSE EXAMINED AT
VANDERBILT HOSPITAL
SYPHILIS CLINIC



RECOGNITION OF EPIDEMICS OF SYPHILIS BY THE PHYSICIAN

The recognition of the epidemic is contingent upon the recognition of early syphilis in an individual. A high level of suspicion and the judicious use of all available diagnostic measures determine not only the difference between possible cure and ultimate disaster, but also, the difference between the control of infectiousness and the infection of others. Every subsequent infection may be the direct responsibility of the physician unless failure to make a diagnosis and to control the patient is unavoidable.

The diagnosis and treatment of the infected person does not terminate the physician's responsibility. The person who seeks medical advice may have been infected by a person devoid of knowledge of syphilis. The patient, in turn, may have unwittingly exposed many others before coming to the physician. As in other epidemic diseases, related cases are frequently found in the families of the infected persons as well as among sexual intimates. The patient, through conversation with his physician, can be convinced of his good fortune in obtaining an early diagnosis and a promise of cure. He can by virtue of his ignorance be freed of the blame of exposing others to the disease. In a short time there may be developed in him a sympathy for others whom he may have exposed or for the one who may have infected him. Candid, sympathetic and informative presentation of the problem to the patient enlists his assistance in bringing in for examination sexual partners and exposed members of his family or at least in a disclosure of names of contacts and a request that the physician assist in giving these the benefit of early diagnosis and treatment.

Theoretically, the incidence of syphilis should be much greater in this group of exposed individuals than in the general population. A study of the results of epidemiological investigation of patients seen in the syphilis clinic of the Vanderbilt University Hospital indicates that this is actually the case (table 1).²

TABLE I

Contacts of 242 Cases of Early Syphilis Seen at the Vanderbilt University Syphilis Clinic
September 1, 1937 to August 31, 1938

	Number		Examined		Positive		Early Syphilis Found	
	Named	Accessible	No.	%	No.	% of Exam.	No.	% of Contacts Exam.
Family Contacts	783	719	565	78.7	155	27.4	98	17.3
Sexual Contacts	294	246	210	85.4	154	73.3	139	66.1
Total	1077	965	775	79.2	309	39.8	237	30.6

During a period of twelve months 242 patients with early syphilis were seen in the syphilis clinic. These individuals disclosed the names of 246

accessible sexual contacts. Of these, 210 (85.4 per cent) were examined and 139 (66.1 per cent) were found to have early syphilis. The examination of 565 (78.7 per cent) of the 719 accessible family contacts of these same patients revealed 155 (27.4 per cent) cases of syphilis of whom 98 had the disease in an early stage. Thus, by the application of epidemiological methods to the 242 cases of early syphilis 237 additional cases were found. Only 36 of these had previously consulted a physician. All were placed promptly under anti-syphilitic treatment.

It is of interest that only 4 (1.6 per cent) of the patients refused to coöperate and only 11 (4.5 per cent) claimed that their exposure had taken place in a house of prostitution. Twelve others claimed lack of knowledge concerning the names of sexual contacts.

There were 139 cases of early syphilis found among the contacts of 144 patients who were able to remember names of sexual partners.

Forty-nine cases of early syphilis were found among spouses of 83 married patients. Of the total marital partners examined 66.2 per cent were proved to have early syphilis (table 2). This is the same percentage

TABLE II
Results of Examinations of Spouses of Patients with Early Syphilis

Number of spouses	Examined		Positive		Found to Have Early Syphilis	
	No.	%	No.	%	Number	% of those examined
83	74	89.2	52	70.3	49	66.2

of early syphilis as among persons named as extra-marital sexual contacts (table 1).

MANAGEMENT OF EPIDEMIC SYPHILIS BY THE PHYSICIAN

The physician is more than a diagnostician and a therapist in the management of any disease. Attention has been directed to the rôle of the physician as a clinical epidemiologist by John R. Paul in his presidential address before the American Society for Clinical Investigation in 1938.³ According to Paul the clinical epidemiologist "starts with a sick individual and cautiously branches out into the setting where that individual became sick—the home, the family; the workshop. He is anxious to search for other members of the patient's family or community group who are actually or potentially ill."

In no other disease is this more applicable than in syphilis. The management of epidemic syphilis depends upon the control of infectiousness not only in the known case but also in cases related to the known case. Success in the control of the known infection is directly proportional to the patient's understanding of his illness.⁴ The informed patient coöperates in carrying

out treatment schedules; the confused or perplexed patient draws his own conclusions as to the time for cessation of treatment and usually the disappearance of signs and symptoms is his criterion of cure. This interpretation permits lapse from treatment long before the minimum requirements to control infectiousness have been satisfied. According to Stokes⁵ 15 per cent of patients with early syphilis who receive less than 20 injections of an arsenical plus an appropriate amount of heavy metal will experience recurrence of infectious lesions. Thus, one of the most important factors in the control of infectiousness is the detailed explanation of the disease to the patient. This has been pointed out by Heller and Smith⁶ and by Exner⁷ and is indicated by our own studies of the effectiveness of patient education.⁸

The attendance records of 100 patients with early syphilis were studied. Fifty of these were seen in the clinic at a time when only casual instruction was given to each patient. The remaining 50 cases were told something about the nature of the disease, its outcome with and without treatment, and other factors intended to afford them a better understanding of their illness. This instruction was given by one individual and was about the same in all instances.

Table 3 shows the advantage of this instruction.

TABLE III
Attendance of Patients with Early Syphilis

	Casual Instruction		Detailed Instruction	
	No.	%	No.	%
Patients Studied	50		50	
Under Treatment 12 Months after Diagnosis	26	52	38	76
Those Receiving Minimum Treatment to Prevent Infectious Relapse (20 Arsenicals)	27	54	40	80
Average Visits, per Patient	27.6		37.4	

When detailed instruction was given, 80 per cent of the patients cooperated sufficiently to meet minimum treatment requirements. When casual instruction was given only 54 per cent met these requirements. The average number of visits of the former group was 37.4 (72 per cent attendance) and of the latter, 27.6 (52 per cent attendance).

Upon the physician rests the responsibility for the discovery of contact infections. The patient alone can identify his exposed contacts. The physician alone can identify the patient. The patient withholds the identity of exposed persons because he is ignorant of the potentialities of the disease. The physician, who is fully aware of these potentialities, should not be a

party to this "conspiracy of silence" and secrecy. He should not adhere to the obsolete notion that his obligation extends no further than his patient.

When the patient has been convinced of his responsibility to others, when he has been freed of blame for exposing others, and when he has been assured that his identity will not be revealed, he should be asked to divulge the names of his contacts during the time which includes the incubation period of the disease. In many instances the patient can be depended upon to bring these contacts to medical attention. In other instances a different approach must be made. In several localities methods similar to those provided for other infectious diseases have been used to assist the medical profession in bringing in for examination the contacts of patients with syphilis. Where such means are not available the local profession might be instrumental in developing them.

Nelson⁹ in Massachusetts employed a trained case worker to do contact and follow-up work for physicians in private practice. This worker, although paid by the Department of Health, acted as an agent of the private physician in the investigation of contacts of his patients. No names were carried back to her office. At the time Nelson instituted this plan (1932) he was able to interest only six of 23 physicians in the venture. Eight of nine contacts whose names were given to the worker for investigation were brought under medical care in a short time. The possibilities of such a plan are apparent.

In New Jersey from 1926 to 1935,¹⁰ 2,295 names of contacts of patients with venereal disease were furnished by physicians to the Bureau of Venereal Disease of the State Department of Health. Examinations were made in 57 per cent (1313) of these cases. Patients themselves were responsible for bringing to examination 268. The Health Department induced the remainder (1,023) to submit to an examination. Syphilis was diagnosed in 946 instances.

The advisability of repeated examinations of the contacts of patients with syphilis cannot be over-emphasized. Variations in the incubation period of early lesions, and in the time of appearance of sufficient reagin in the blood, make it imperative that reexaminations be made for skin and mucous membrane lesions and that serologic tests be repeated at frequent intervals during the three month period following the last exposure to infection.

SUMMARY AND CONCLUSIONS

Syphilis is an epidemic disease. The recognition of this is one of the responsibilities of the physician. The management of the epidemic is in his hands. By means of education he may convince his patient of the need for continued treatment and thus prevent the spread of the disease from one reservoir of infection. The patient alone can identify the exposed contacts who may have become infected and who may be responsible for the further spread of the disease.

Successful methods have been formulated to investigate persons who have been designated as contacts. Where such methods have not been made available the physician may effectively assist in their development.

This is a new field for the clinician. It is one referred to by Paul³: "If these fields are eventually to be investigated, it is the man with clinical judgment who can best blaze the trail, for it is the prime responsibility of the clinician to do the work. It is his responsibility far more than that of the public health man, or the bacteriologist, or the chemist. To do this the clinician will, however, have to adopt a new technic and a new uniform."

BIBLIOGRAPHY

1. GILL, A. G.: The genesis of epidemics, 1928, William Wood and Co., New York, Chapter I.
2. CLARK, E. G.: Results of contact investigation in a University Hospital syphilis clinic. To be published.
3. PAUL, JOHN R.: Clinical epidemiology. President's Address, Jr. Clin. Invest., 1938, xvii, 539.
4. NELSON, N. A.: Syphilis looks at the doctor, New England Jr. Med., 1937, ccxvii, 971.
5. STOKES, J. H.: Cutaneous and mucosal relapse in early syphilis and its differentiation from reinfection, Ven. Dis. Inform., 1931, xii, 55.
6. HELLER, J. R., and SMITH, D. C.: Proper epidemiological approach in early cases of syphilis decreases treatment delinquency, Indian Jr. Ven. Dis., 1937, iii, 155.
7. EXNER, M. J.: The value of instructing the syphilis patient, Ven. Dis. Inform., 1935, xvi, 59.
8. CLARK, E. G.: Patient instruction in controlling infectiousness of patients with early syphilis. To be published.
9. NELSON, N. A.: The follow up of gonorrhea and syphilis in private practice, New England Jr. Med., 1933, ccviii, 1153.
10. INGRAHAM, N. R.: Contact tracing and case holding in New Jersey, Ven. Dis. Inform., 1938, xvix, 61.

ANAPHYLAXIS AND ALLERGY *

By CARL A. DRAGSTEDT, Ph.D., M.D., *Chicago, Illinois*

PROBABLY the first definite suggestion that clinical allergy is related to experimental anaphylaxis was made by Wolff-Eisner¹ in 1905. Since that time numerous workers have noted both the fundamental similarities and the apparent differences between these reactions. The similarities may be stated in general terms as follows: In both instances reactions are produced by substances which may or may not have any inherent toxicity; the reactions occur in sensitive or susceptible individuals; the severity of the reaction depends more upon the degree of that susceptibility than upon either the inherent toxicity or the dose of the substance producing it; and the character of the reaction is related to the susceptibility of the individual and is not a specific property of the provoking substance. The apparent differences may be stated as follows: Anaphylaxis is invariably dependent upon a known sensitization to an antigen which is usually protein in nature while allergy may apparently exist without recognizable sensitization and be related to non-protein substances. In anaphylaxis the sensitive state is relatively temporary while in allergy it tends to persist throughout life. The anaphylactic reaction involves an antigen-antibody reaction while the allergic reaction may or may not involve recognizable antibodies. Lastly an anaphylactic reaction may be followed by a state of complete refractoriness while the allergic reaction is followed by only a partial desensitization.

The reaction of anaphylaxis and its relationship to immunity is sufficiently intriguing in its own right to have prompted a prodigious amount of study and investigation. I think it probable, however, that many workers have been stimulated with the hope that a partial or complete solution of the experimental problem would contribute to the solution or management of the clinical problem. It is with such a hope that I discuss this question. Within recent years a partial solution of the anaphylaxis problem, with respect to its mechanism, has been made. It seems not untimely to consider the implications of this work, so I wish to present a brief résumé of its development.

In 1910 Manwaring² reported some experiments in which a cross circulation was established between a normal dog and a sensitized animal. He reported that the injection of the antigen into the latter resulted in anaphylactic symptoms in both animals and concluded that some blood-borne agent was necessarily implied as the mediator of the symptoms to the normal animal. At about this same time Dale and Laidlaw³ called attention to the similarities between histamine intoxication and anaphylactic shock so

* Received for publication April 10, 1939.

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that inferences as to the chemical nature of the blood-borne agent in anaphylactic shock can be said to date from this period. In 1917, however, Weil⁴ virtually dispelled all hopes of this kind of a solution to the anaphylaxis problem. He challenged the validity of cross circulation experiments by pointing out that a marked fall in blood pressure in one animal from any cause would necessarily cause a similar fall in the other by the simple process of exsanguination and also that suggestive results were frequently probably due to incompatibilities between the bloods of the two animals. He also reported that withdrawing blood from anaphylactic animals and injecting it into normal animals had negligible effects. He concluded that a humoral theory of anaphylaxis was untenable. The weight of his authority was such that conflicting evidence was largely disregarded for a considerable time. As a by-product of his work it became rather generally accepted that the important reaction in anaphylactic shock is not the reaction between the antigen and the circulating antibodies, but the reaction between the antigen and the fixed tissue cells.

In 1925 Manwaring, Hosepian, O'Neill and Moy⁵ reported some interesting and suggestive experiments. They vascularly anastomosed the hind quarters of a normal dog to a sensitized one and noted that the urinary bladder and intestine of the normal animal contracted when anaphylactic shock was induced in the sensitized animal. Since this could not be explained by the nonspecific effect of the fall in blood pressure, it seemed necessary to interpret some smooth muscle stimulating agent as being concerned. Because of some negative experiments with supposedly immunized tissues they⁶ were led to conclude that the agent was a sort of secondary antigen presumably of protein nature.

Meanwhile the studies of Abel and Kubota⁷ and of Best, Dale, Dudley and Thorpe⁸ had shown that histamine is a normal constituent of many tissues, and Lewis⁹ had reported circumstantial evidence indicating that a histamine-like substance is apparently liberated in the skin by certain kinds of injury. Considering the evidence available at the time, Dale in 1929¹⁰ reaffirmed the histamine theory of anaphylaxis. Experiments to substantiate this theory were soon forthcoming. In 1930 and 1931 Watanabe¹¹ showed that the content of histamine-like substance in guinea-pigs' lungs and in dogs' livers is strikingly decreased when these respective animals are subjected to anaphylactic shock. In 1932 Dragstedt and Gebauer-Fuelnegg¹² reported the detection of a histamine-like substance in the blood and lymph of dogs during anaphylactic shock and Bartosch, Feldberg and Nagel¹³ found a similar substance in the perfusate from guinea-pigs' lungs. In 1936 Dragstedt and Mead¹⁴ reported the definite identification of the histamine-like substance as histamine. Of more importance they¹⁵ showed that in the dog the amount of histamine liberated during the anaphylactic reaction is adequate to account for the severity of the reaction and is thus a definitely operating factor and not just an incidental by-product. That histamine is liberated during the anaphylactic reaction in dogs and in

guinea-pigs has now been confirmed by a number of workers,¹⁶ so that it can definitely be stated that the histamine theory has been verified in more than one animal species.

During the last two years, Eagle, Johnston and Ravdin¹⁷ and Waters, Markowitz and Jacques¹⁸ have proved that the incoagulability of the blood which occurs during anaphylactic shock is due to the liberation from the liver of an anticoagulant probably identical with heparin. It is thus clear that the dominant manifestations of anaphylactic shock in experimental animals are attributable to recognizable agents which were initially contained within the fixed tissue cells of the sensitive animal and which were discharged from these cells in some manner subsequent to the injection of the antigen.

Since these results are so readily demonstrated with methods now available it seems appropriate to comment on the negative results of Weil and others who have looked for active agents in the blood of anaphylactic animals. Weil reported that exsanguinating dogs during anaphylactic shock and transfusing the blood into normal animals gave negative results. On studying the protocols of Weil's experiments, his negative results are readily understood. Blood collections were never made less than 20 minutes after the shocking dose of serum and in most instances considerably later. The transfusions were then made into animals under ether, which would mask the minor symptoms of vomiting, etc., while no records of blood pressure effects were made. Also of importance is the fact that the blood was injected slowly and intermittently over a period of a half-hour or so. We now know that the histamine is liberated promptly after injection of the antigen and that it then disappears very rapidly from the plasma of the circulating blood. Consequently there was probably little or no activity in the blood samples that he tested in addition to the fact that his method of determining activity was not at all delicate. The negative results of other investigators have in general a similar explanation.

I have purposely stressed these remarks because a number of recent writers on the subject of anaphylaxis have failed to appreciate the definitive character of the experimental evidence that has been reported. It should also be pointed out that the present evidence respecting the rôles of histamine and heparin as secondary operating agents in anaphylactic shock, does not exclude the possibility of other presumably less significant agents being similarly liberated and related to certain features of the symptomatology.

Having worked out technics by which agents responsible for the major manifestations of anaphylactic shock could be detected and incriminated, the attention of various investigators was directed to various other intoxications having some similar aspects in symptomatology. Experimental evidence of various kinds has accumulated which indicates that certain snake venoms,¹⁹ bee venom,²⁰ staphylococcal toxin,²¹ as well as certain inorganic poisons such as mercuric chloride,²² can produce a cellular injury which results in a liberation of histamine. For some of these the circumstantial

evidence that the liberated histamine is a contributory factor in the symptomatology is fairly convincing. With others the direct toxicity of the substance obscures any such analysis. We²³ have made an extended study of peptone reactions and since in this instance there is no complicating factor of direct toxicity on the part of the substance which provokes the reaction, I shall deal with this in more detail. The intravenous injection of peptone solutions into dogs results in a reaction which is virtually indistinguishable from that occurring in acute anaphylactic shock. We have been able to demonstrate that this reaction is accompanied by and due to the liberation of histamine just as is the case in anaphylactic shock. This has now been confirmed.²⁴ Also it has been reported by Quick²⁵ and by Waters, Markowitz and Jacques¹⁸ that heparin is likewise liberated during the peptone reaction. Thus it is clear that peptone shock is similar to anaphylactic shock in mechanism as well as in its symptom complex.

If the general similarity between experimental anaphylaxis and clinical allergy has been considered sufficiently close to warrant the hope that lessons learned from the former could be applied to the latter, it seems equally appropriate to view such reactions as that of peptone as having their clinical counterparts. A consideration of some of the characteristics of peptone reactions suggests that in some respects they are more closely comparable with corresponding features of certain allergic reactions than is the anaphylactic experiment. It has long been known that for the production of peptone shock, no preceding sensitization procedure is necessary. The sensitivity occurs spontaneously and so far as has been determined is not dependent upon antibodies of any sort. A certain percentage of animals (approximately 10 per cent of dogs in our experience) is naturally refractory, or conversely it can be said that a certain percentage of animals is spontaneously sensitive. We have recently found that newly born puppies may be sensitive as well as very old dogs, so that the sensitivity in a given animal presumably tends to last throughout life. The injection of a peptone solution is followed by a limited degree of desensitization which differs from that in the anaphylactic experiment by being less regularly produced, less complete and of shorter duration. These features of the peptone reaction have a surprising similarity to the characteristics of certain allergic reactions which have been listed as differentiating the latter from experimental anaphylaxis.

The evidence indicates that various substances may produce directly the same kind of cellular injury and after effects as can be produced by antigens acting indirectly through antibody reactions. Certain experimental reactions of this sort have a greater resemblance to the clinical reaction of allergy than has the anaphylactic experiment. If reasoning by analogy is warranted, this means that we must view these reactions as a whole and that we can not necessarily expect to modify or control all of them by the same methods.

I would therefore like to schematize these reactions for the purpose of

considering some of the various theoretical methods of modifying or controlling them that such a schema suggests.

- A.* Antigenic allergen—via antibodies—acts on sensitive cells to liberate histamine, heparin and possibly other agents, which in turn act on responsive or reacting cells to produce characteristic effects.
- B.* Non-antigenic allergen acts on sensitive cells to liberate histamine, heparin and possibly other agents, which in turn act on responsive or reacting cells to produce characteristic effects.

I am visualizing Schema *A* as applying to experimental anaphylactic shock as well as certain allergic reactions and Schema *B* as applying to experimental peptone shock and certain other allergic reactions. In this schematization the term "allergen" is used with reference to any substance which may provoke reactions of this type and is not synonymous with the term "antigen" which implies a capacity to stimulate antibody formation. The term "sensitive cell" refers to those cells with which the allergen reacts, and the term "responsive cell" refers to those cells, etc., upon which the liberated products from the sensitive cells react. It is very likely that in many instances the sensitive cells are identical with the responsive cells. At first glance there may be something anomalous in the conception of a cell containing in its interior a physiologically active substance which produces no effect until it goes outside the cell, when it may then profoundly influence its former abode. There is nothing startling about this, however, for from what we know about the mode of action of drugs upon cells, in most instances it seems likely that they act upon cells by producing effects upon the cell surface. It has been experimentally demonstrated, for example, that certain drugs may be injected intracellularly without producing the effects which they readily do when applied to the cell surface.

Assuming that a chain reaction of this kind may be vulnerable at any link, it should theoretically be possible to modify or control the reaction by procedures which primarily affect (1) the allergen, (2) the antibodies, (3) the sensitive cells, (4) the liberated products, or (5) the responsive cells. By eliminating or altering the allergen the reaction is avoided rather than modified or controlled. The usual desensitization procedure probably acts upon or through the antibody mechanism. That it is not invariably successful suggests the possibility that some of the reactions in which it fails may belong to a non-immunologic category such as we have indicated. If so, it seems important to consider the theoretical possibilities with respect to the third, fourth and fifth links in the chain. With respect to the sensitive cells it is theoretically possible to breed them out, excise them, alter their permeability, or deplete their store of active substances. With respect to the liberated agents it is theoretically possible to inactivate or neutralize them. With respect to the responsive cells it is theoretically possible to render them insusceptible to the liberated agents either by the development of an acquired tolerance or by preëmpting the cell receptors with a chemically similar but physiologically inactive blockading substance. Or it is

possible to use drugs which are pharmacological antagonists to the liberated products and which either reduce the reactivity of the responsive cells or influence them in opposite directions.

It has been an interesting study to go through the long lists of agents which have been reported to be beneficial in experimental anaphylaxis and in clinical allergies respectively. It has long been recognized that these diverse substances have had no single common denominator of pharmacological action. This very fact seems to me to substantiate the theory that these reactions have several and varied vulnerable sectors. With the schemata outlined here an intelligible answer can be given in many instances as to why totally dissimilar substances have shown more or less equivalent beneficial effects. A critical survey of the literature indicates that most of the therapeutic agents employed have had only a limited effectiveness. Many of them have been employed purely empirically, however, and perhaps with a better understanding of the purpose for which they are used, better results may be obtained. It is also clear that a number of the theoretical possibilities suggested here have not as yet been explored. Some of them, to be sure, are neither practical nor feasible, but it may be hoped that others may afford some additional means of modifying or controlling these puzzling reactions.

SUMMARY

There is experimental evidence to indicate that certain foreign substances, not necessarily protein in nature, can produce the same kind of reactions in experimental animals upon their initial administration, as are produced by antigenic agents after a prior sensitization. The possibility that some of the allergic reactions seen clinically are similarly provoked directly by foreign substances is visualized, and the implications of this upon the problem of management are suggested.

BIBLIOGRAPHY

1. WOLFF-EISNER, ALFRED: *Das Heufieber, sein Wesen und seine Behandlung*, 1906, J. F. Lehmann Company, Munich.
2. MANWARING, W. H.: *Der physiologische Mechanismus der anaphylakteschen Shocks*, *Ztschr. f. Immunitätsf.*, 1910, viii, 1-23.
3. DALE, H. H., and LAIDLAW, P. P.: *The physiological action of B-Iminazolyethylamine*, *Jr. Physiol.*, 1911, xli, 318-344.
4. WEIL, RICHARD: *Studies in anaphylaxis. XXI. Anaphylaxis in dogs. A study of the liver in shock and in peptone poisoning*, *Jr. Immunol.*, 1917, ii, 525-556.
WEIL, RICHARD, and EGGLESTON, C.: *Studies in anaphylaxis. XXII. Anaphylactic reactions of the isolated dog's liver*, *Jr. Immunol.*, 1917, ii, 571-572.
5. MANWARING, W. H., HOSEPIAN, V. M., O'NEILL, F. I., and MOY, H. B.: *Hepatic reactions in anaphylaxis. X. The hepatic anaphylatoxin*, *Jr. Immunol.*, 1925, x, 575-581.
6. MANWARING, W. H., REEVES, D. L., MOY, H. B., SHUMAKER, P. W., and WRIGHT, R. W.: *Relation of anaphylaxis to immunity. II. The phenomenon of antianaphylatoxic immunity*, *Jr. Immunol.*, 1927, xiii, 63-67.
7. ABEL, J. J., and KUBOTA, S.: *On the presence of histamine (B-Iminazolyethylamine) in the hypophysis cerebri and other tissues of the body and its occurrence among the hydrolytic decomposition products of proteins*, *Jr. Pharm. and Exper. Therap.*, 1919, xiii, 243-300.

8. BEST, C. H., DALE, H. H., DUDLEY, H. W., and THORPE, W. V.: The nature of the vaso-dilator constituents of certain tissue extracts, *Jr. Physiol.*, 1927, lxi, 397-417.
9. LEWIS, THOMAS: Blood vessels of the human skin and their responses, 1927, Shaw and Sons, Ltd., London.
10. DALE, H. H.: Croonian lectures on some chemical factors in the control of the circulation, *Lancet*, 1929, ccxvi, 1285-1294.
11. WATANABE, K.: Quantitative Untersuchungen über die pharmakologisch Wirksamen alkohollöslichen Stoffe der Meerschweinchenlunge und -leber, *Ztschr. f. Immunitätsf.*, 1930, lxix, 117-125.
WATANABE, K.: Quantitative Untersuchungen über den Gehalt an Darmkontrahierenden Stoffen von Lunge und Leber bei Meerschweinchen im Stadium der Eiweissensibilisierung und im anaphylaktischen Shock, *Ztschr. f. Immunitätsf.*, 1931, lxxii, 50-56.
12. DRAGSTEDT, C. A., and GEBAUER-FUELNEGG, ERICH: Studies in anaphylaxis. I. The appearance of a physiologically active substance during anaphylactic shock, *Am. Jr. Physiol.*, 1932, cii, 512-519. II. The nature of a physiologically active substance appearing during anaphylactic shock, *Am. Jr. Physiol.*, 1932, cii, 520-526.
13. BARTOSCH, R., FELDBERG, W., and NAGEL, E.: Das Freiwerden eines Histaminähnlichen Stoffes bei der Anaphylaxie des Meerschweinchens, *Pflüger's Arch. f. d. ges. Physiol.*, 1932, ccxxx, 129-153.
14. DRAGSTEDT, C. A., and MEAD, F. B.: Further observations on the nature of the active substance ("Anaphylatoxin") in canine anaphylactic shock, *Jr. Immunol.*, 1936, xxx, 319-326.
15. DRAGSTEDT, C. A., and MEAD, F. B.: The rôle of histamine in canine anaphylactic shock, *Jr. Pharm. and Exper. Ther.*, 1936, lvii, 419-426.
16. UNGAR, G., and PARROTT, J. L.: Mise en évidence «in vitro» de la libération de substances histaminiques dans le choc anaphylactique, *Ann. de Physiol.*, 1937, xiii, 939-942.
CODE, C. F.: The blood histamine in anaphylactic shock, *Am. Jr. Physiol.*, 1938, cxxiii, 40-41.
17. EAGLE, H., JOHNSTON, C. G., and RAVDIN, I. S.: On the prolonged coagulation time subsequent to anaphylactic shock, *Johns Hopkins Hosp. Bull.*, 1937, lx, 428-438.
18. WATERS, E. T., MARKOWITZ, J., and JACQUES, L. B.: Anaphylaxis in the liverless dog, and observations on the anticoagulant of anaphylactic shock, *Science*, 1938, lxxxvii, 582-583.
19. FELDBERG, W., and KELLAWAY, C. H.: Liberation of histamine from the perfused lung by snake venoms, *Jr. Physiol.*, 1937, xc, 257-279.
DRAGSTEDT, C. A., MEAD, F. B., and EYER, S. W.: Rôle of histamine in circulatory effects of rattlesnake venom (Crotalin), *Proc. Soc. Exper. Biol. and Med.*, 1938, xxxvii, 709-710.
20. FELDBERG, W., and KELLAWAY, C. H.: Liberation of histamine and its rôle in the symptomatology of bee venom poisoning, *Australian Jr. Exper. Biol. and Med. Sci.*, 1937, xv, 461-489.
21. FELDBERG, W., and KEOGH, E. V.: Liberation of histamine from the perfused lung by staphylococcal toxin, *Jr. Physiol.*, 1937, xc, 280-287.
22. FELDBERG, W., and KELLAWAY, C. H.: The liberation of histamine by staphylococcal toxin and mercuric chloride, *Australian Jr. Exper. Biol. and Med. Sci.*, 1938, xvi, 249-259.
23. DRAGSTEDT, C. A., and MEAD, F. B.: Peptone shock, *Jr. Pharm. and Exper. Therap.*, 1937, lix, 429-436.
DRAGSTEDT, C. A., and MEAD, F. B.: Further observations on peptone shock, *Jr. Pharm. and Exper. Therap.*, 1937, lx, 105.
24. TINEL, J., UNGAR, G., and PARROTT, J.-L.: Sur l'histaminémie plasmatique et globale, son évolution au cours du choc peptonique du chien, *Compt.-rend. soc. de Biol.*, 1938, cxxix, 267-269.
25. QUICK, A. J.: On the coagulation defect in peptone shock, *Am. Jr. Physiol.*, 1936, cxvi, 535-542.

THE VALUE AND SIGNIFICANCE OF THE TUBERCULIN TEST *

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THE tuberculin test is today a commonly employed procedure. As an aid in the diagnosis of tuberculosis, it is being used routinely by the specialists, the general practitioners, and by those concerned purely with the preventive aspect of the disease. Mass testing was first introduced by the veterinarians in their search for bovine tuberculosis in herds. Mass testing of groups of the population is at present an indispensable feature of most antituberculosis programs.

As a test for tuberculosis, tuberculin has been employed in a variety of ways. At first it was given subcutaneously. The ophthalmic test of Calmette and Wolff-Eisner in which tuberculin was applied to the conjunctiva was discarded in preference to Moro's inunction test. Several modifications of this test are now being advocated on the grounds of simplicity of technic and to avoid lay objection to the distasteful needle. The patch test is now gaining in popularity.¹ In sensitivity the patch test corresponds to the Pirquet or to a Mantoux dilution of 1-10,000. The use of one strength tuberculin and the questionable absorption of tuberculin through a thickened epidermis fog the accuracy of this test. A negative patch test should be followed by a test using second strength P.P.D. At present the von Pirquet and the Mantoux are the most frequently used methods. The Pirquet is done by scarification of the skin under full strength tuberculin. The Mantoux is performed intradermally with diluted tuberculin. It is more exact than the Pirquet as the quantity can be accurately measured. It also gives a better cosmetic result. It has been said that the Pirquet is reliable in disclosing past tuberculous infections of a nature to provoke radiographically demonstrable lesions in the chest; whereas, the Mantoux test may be positive in the absence of any demonstrable infection.² In the Florida program, we use the Mantoux intradermal test with P.P.D. in two strengths exclusively.

Formerly, old tuberculin, known as O.T., was injected in dilutions varying from 1 in 10,000 to 1 in 100. O.T. was first introduced by Koch in 1890—eight years after the discovery of the tubercle bacillus. It is an exotoxin in the form of a filtrate obtained from a culture of virulent human type bacilli in bouillon. The presence of non-specific protein in the form of peptones is likely to cause pseudo-reactions.

* Received for publication May 16, 1938.

Presented at Polk County Medical Society, Lakeland, Florida, January 12, 1938; Suwannee River Medical Society, Mayo, Florida, February 11, 1938; The Annual Conference of The Florida Tuberculosis and Health Association, Orlando, Florida, April 26, 1938; Duval County Medical Society, Jacksonville, Florida, May 2, 1938.

Consequently, we are now employing purified protein derivative tuberculin, called P.P.D. It can be obtained in five, ten, or one hundred test sizes. It is marketed in tablet form in two strength doses with a sterile buffered diluent, consisting of normal saline and 1 per cent phenol, to be added at the time of its use. The first strength (0.00002 mg.) is the initial dose and is equivalent to a 1:25,000 dilution of O.T. If no reaction is obtained, the second strength (0.005 mg.) is employed. The latter is 250 times as strong as the first strength. Dilutions of P.P.D. will keep for three days on ice, but should then be discarded. P.P.D. is favored over O.T. because of its greater efficiency and because it is a purified and more easily standardized material. Dr. Esmond Long of the Phipps Institute in Philadelphia is working on a suitable single dose preparation of P.P.D. which will obviate the necessity for two strength tests.

The technic of the Mantoux intradermal test is similar to that of the Schick test. The skin on the flexor surface of the forearm is cleansed with 95 per cent alcohol and allowed to dry. A 1 c.c. tuberculin syringe is used. The syringe should be used only for that purpose. No matter how well sterilized, a syringe which has been employed for the tuberculin test will often produce false reactions if used for the Schick test. A needle with a sharp short bevel, gage 26, is best. The needle is inserted almost parallel to the skin and 0.1 c.c. of the tuberculin is injected. This will produce a small white bleb showing that the injection has been made into the skin and not under it. If the injection is made subcutaneously, no local reaction may appear and a generalized febrile reaction may result. No dressing need be applied to the area.

The site should be examined in 48 hours. The reaction, if any, appears in 12 to 24 hours; reaches its maximum in 48 hours; and tends to disappear gradually after 72. Pseudo-reactions usually appear sooner. Reactions reaching a maximum after 72 hours are usually due to superimposed infection caused usually by scratching. If such infection has occurred, the usual signs of lymphangitis and adenitis may be observed. Often, a purely erythematous reaction may occur after 72 to 96 hours.

A positive tuberculin reaction is a red edematous area at the site of injection. Erythema, in itself, does not constitute a positive result. There must be induration, at least five mm. in its shortest diameter, before a reaction can be called truly positive.³ This can be felt as an area elevated over the surface of the surrounding skin. As the relationship between the intensity of the reaction and the degree of tuberculous activity, the time of infection, or the clinical course which the disease will pursue has not been proved, it is not necessary to classify the intensity or degree of the positive reaction. A reaction is positive, negative or doubtful. A positive reaction indicates that tuberculo-allergy is present; that is, that the tissues are hypersensitive to the products of the bovine or human type tubercle bacillus.

To appreciate the full significance of a positive tuberculin reaction, it is necessary to review briefly the pathogenesis of tuberculosis.

There are two types of tuberculosis: the childhood and the adult. As either of these types may occur in children or adults, it would be less confusing to refer to them as the first infection type and the reinfection type respectively. The reinfection type will not occur unless there has been a previous first infection type regardless of the age of the individual.

We are born free of tuberculosis as the disease is not inherited. When tubercle bacilli invade the body for the first time, a series of changes occurs. The lipid capsules of the bacilli are dissolved liberating tuberculo-protein. With liberation of this substance, the tissues are sensitized. This period may last from two to six weeks after which a positive tuberculin test can be secured.⁴ The tissues become allergic and will react in a hypersensitive manner to further contact with tuberculo-protein.

Entrance of the bacilli may be effected through any of the avenues of the body but, by means of inhalation, the lung is the commonest portal. The organisms are carried to the subpleural surface of the lung parenchyma and tubercle formation takes place there, producing what is known as the Ghon tubercle. The glands at the hilum draining that area soon become involved in the process. This constitutes the primary complex. It takes two to six weeks to develop and is a pathognomonic morphological entity. It occurs only once in each body and marks the first entrance of the bacilli.⁵ This series of changes is the genesis of the first infection type of tuberculosis. The condition is really a pulmonary tuberculosis, but usually runs a benign course if further infection stops and general resistance is maintained. Calcification occurs and no permanent damage results. But it is well to remember that living bacilli may be incorporated in the calcified matrix which, many years afterwards, may be the source for reinfection. It usually takes two to four years for calcification to cast a recognizable shadow on the roentgen-ray.⁶ Consequently, a negative chest plate in a positive tuberculin reactor may be due to the fact that the time element has not been sufficient for the lesion to become manifest radiographically. The tuberculin test with P.P.D. detects approximately three-fifths of all cases of primary tuberculous infection. The roentgen-ray is only slightly more efficient on a percentage basis.

The reinfection type of tuberculosis may occur immediately following the first infection or many years later by endogenous or exogenous reinfection. The soil is no longer virgin. Now, the tissue is allergic, and in the presence of tuberculo-protein, will flare up in an outrageous manner. The amount of tissue destruction will depend upon the virulence and dosage of the organisms and upon the resistance and immunity of the host. This is the classical type of tuberculosis, with caseation and cavitation.

Once the tuberculin test is positive it usually remains so throughout life, although the degree of the reaction may vary from time to time. The tuberculin reaction may even show a daily variation apparently due to periodic changes in vascular and tissue permeability.⁷ However, the test may become absolutely negative under certain conditions. In the acute

stages of measles and scarlet fever, sensitivity to tuberculin may be greatly decreased or completely absent. This anergy may last one to two weeks after the rash appears.⁸ During pregnancy anergy may be present. In very acute tuberculosis and in moribund cases,⁹ the resistance is exhausted and the tissues are flooded with tuberculo-protein to such a degree that the tuberculin test will elicit no response. During the incubation or latent period when the primary complex is forming the test will be negative. About 5 per cent of individuals will show radiographic evidence of old tuberculous foci and a negative tuberculin reaction. This anergy is probably due to lesions long healed in which the calcified foci contain no living organisms.¹⁰ As calcification and healing take place, there is a decrease in the allergic response.¹¹ Hence, in the latter stages of the primary infection, a feeble cutaneous reaction to tuberculin, denoting a low degree of tuberculous allergy, is generally obtained. A test followed by a general reaction (febrile, etc.) is suggestive of an active tuberculous lesion.

A positive test tells us that tubercle bacilli have invaded the body—tuberculous infection has been established—but it does not tell us if destructive disease is present. It indicates with certainty that the first infection type has occurred but to discover the presence of reinfection type a roentgen-ray of the chest is necessary. We know the superiority of the roentgen-ray over other methods of examination in arriving at a diagnosis of early tuberculosis. Consequently, all positive tuberculin reactors should be roentgenographed.

The tuberculin test should be used for the recognition of infection at the earliest possible moment. If every child were tested periodically from infancy, the time and source of the infection could easily be ascertained.¹² It is for this reason that we recommend physicians to make the test a routine part of the examination of all children. If the test is negative it should be repeated at least once yearly until the adolescent period is passed. The interval between the last negative and first positive reaction is the time when the child was exposed to and infected by an open case of tuberculosis. By tuberculin testing and roentgen examination of the child's contacts, the unknown or unrecognized case can be discovered at a curable stage and a stop put to the further spread of the disease. Objection to repeated tuberculin testing on the grounds of possible sensitization of the child to tuberculo-protein has been raised. However, such sensitization from the ordinary use of tuberculin for skin testing purposes does not appear likely,¹³ although it may increase an already existing slight sensitivity.¹⁴ At times the site of a previous test in a positive reactor may show erythema following a re-test in some other area months afterwards. In the larger northern cities, the incidence of positive reactions is the following: at five years of age 15 per cent react, at seven years 20 per cent, at ten years 40 per cent. The rates are much lower in most southern states.¹⁵ In this state we have tested nine thousand school children from 15 to 20 years of age. In the white group 29 per cent were positive reactors. The rate for the negro

group was 10 per cent higher. Almost 2 per cent of these positive reactors showed roentgen evidence of reinfection type tuberculosis.

In infants and children up to four years of age a positive reaction can be taken as a sign of a relatively active process, since it takes two to four years for the lesion to become arrested.^{16, 17} The tuberculosis mortality rate in this age group is very high as these children are practically without defense against infection and reinfection, living, as they do in most cases, with a tuberculous parent.¹⁸ A study of infants under two years of age with positive reactions gave these results: 13 per cent of the white and 31 per cent of the colored infants died within five years. Seventy per cent of these deaths occurred within the first year of observation.¹⁹

Above five years of age there is greater opportunity for extrafamilial exposure. However, the home and the school must be considered the most fertile sources of the infection. It is there that prolonged and intimate exposure to massive dosage of bacilli is most likely to take place.

As we ascend the age groups we find that the tuberculosis morbidity rate increases proportionately with age; whereas, the mortality rate remains fairly low until puberty when it accelerates until it reached a peak in the 20 to 35 year age period.

A school child with a positive tuberculin test is 27 times more likely to develop a manifest reinfection lesion than a colleague without primary infection.²⁰ Children under five years with positive reactions should be supervised for a time sufficient to indicate by roentgen-ray that no lesion exists—usually until seven years of age if the source of the infection has been removed. If the source still exists supervision should be continued until 25 years of age. Adolescents and young adults 15 to 20 years old with positive reactions and a history of exposure to an open case within two years should be observed until they are 25 regardless of roentgen findings.²¹ It would be best if all positive reactors with negative chest plates were to be refilmed yearly until the adolescent stage was past.

Dr. J. A. Myers, president of the National Tuberculosis Association, believes that the best criterion of the tuberculosis problem in any state is the incidence of positive tuberculin reactors rather than morbidity and mortality rates.

The tuberculin test is of great value in differential diagnosis. It has been said that, except in the anergic group, a negative test rules out tuberculosis as definitely as tubercle bacilli in the sputum rule it in.²⁰

Tuberculin testing is of such practical importance that it is ranking in general practice equally with small pox vaccination and the Schick test.

REFERENCES

1. VOLLMER, H., and GOLDBERGER, E. W.: New tuberculin patch test, *Am. Jr. Dis. Child.*, 1937, liv, 1019-1024.
2. SCHEEL, O.: Tuberculin reactions compared with roentgen findings in lungs, *Nord. med. tidskr.*, 1937, xii, 761-763.

3. GOLDBERG, B.: Clinical tuberculosis, 1935, F. A. Davis Company, Philadelphia.
4. TYSON, R.: Certain significant aspects of childhood tuberculosis, *Jr. Am. Med. Assoc.*, 1937, cix, 753-755.
5. PINNER, M.: The pathology of the primary complex, *Bull. Am. Acad. Tuberc. Phys.*, 1937, i, 10-14.
6. CHADWICK, H. D.: Tuberculosis in children and adolescents, *Jr. Michigan Med. Soc.*, 1932, xxxi, 109-113.
7. HOWE, J. S.: Daily variations in tuberculin reactions; relation to vascular pressor episode, *Am. Rev. Tuberc.*, 1938, xxxvii, 273-285.
8. DODDS, G. A.: The present status of the tuberculin reaction, *Jr. Lancet*, 1937, lvii, 12-15.
9. ARONSOHN, M. H., and ORNSTEIN, G. G.: Allergy and bacilleemia in pulmonary tuberculosis, *Quart. Bull. Sea View Hosp.*, 1936, i, 187-195.
10. OPIE, E. L., and MCPHEDRAN, F. M.: Organization of outpatient tuberculosis clinic for epidemiological investigation, *Am. Jr. Hyg.*, 1935, xxii, 539-564.
11. JOHNSTON, J. A., HOWARD, P. J., and MARONEY, J.: Quantitative study of tuberculin reaction in childhood tuberculosis, *Am. Rev. Tuberc.*, 1934, xxix, 652-659.
12. SIR ROBERT PHILIP: Personal communication, February, 1937.
13. NELSON, W. E., MITCHELL, A. G., and BROWN, E. S.: Possibility of sensitization to tuberculin, *Am. Rev. Tuberc.*, 1938, xxxvii, 286-310.
14. McCARTER, J., GETZ, H. R., and STIEHM, R. H.: Comparison of intracutaneous reactions in man to purified protein derivatives of several species of acid-fast bacteria, *Am. Jr. Med. Sci.*, 1938, cxcv, 479-493.
15. SIDBURY, J. B.: Tuberculosis in childhood, *Jr. So. Med. Assoc.*, 1937, xxxi, 769-772.
16. SCHICK, B.: Allergy and immunity, *Radiol. Rev. and Mississippi Valley Med. Jr.*, 1937, lix, 1-7.
17. KAYNE, G. G.: Mantoux test in children with special reference to home contacts, *Brit. Jr. Child. Dis.*, 1936, xxxiii, 20-31.
18. LEES, H. D.: Tuberculous infection, *Bull. Am. Acad. Tuberc. Phys.*, 1937, i, 17-20.
19. BRAILEY, M.: Mortality of tuberculin positive infants, *Milbank Quart.*, 1937, xv, 37-54.
20. MORRIS, E.: Tuberculin testing, *Bull. Am. Acad. Tuberc. Phys.*, 1937, i, 3-7.
21. EDWARDS, H. R.: Clinic standards and clinic practice, *Am. Rev. Tuberc.*, 1937, xxxvi, 592-601.
22. LICHTENSTEIN, M. R.: Value of negative intracutaneous tuberculin (Mantoux) test in adults, *Am. Rev. Tuberc.*, 1934, xxix, 190-197.

THE RELATIVE VALUE OF THE BASAL METABOLIC RATE, VELOCITY OF BLOOD FLOW AND CREATINE TOLERANCE TEST IN THE DIFFERENTIAL DIAGNOSIS OF GRAVES' DISEASE AND ALLIED CONDITIONS *

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THE differential diagnosis of Graves' disease from a group of conditions, which occasionally simulate it in symptomatology, not infrequently presents a difficult problem. Whereas typical cases of Graves' syndrome present no difficulty, since the clinical picture is so characteristic, borderline cases in which the symptomatology is not clearly delineated are not so easy to differentiate. We refer to cases of inactive Graves' disease, autonomic imbalance, menopause with autonomic imbalance and hypertension, simple goiter and cases of essential hypertension.

Because these cases are not as readily diagnosed on clinical grounds, efforts have been made by previous workers to find some objective laboratory determination which would simplify the differentiation of these cases from true instances of Graves' syndrome. The finding most commonly relied upon has been the determination of the basal metabolic rate. More recently there has been introduced by Shorr the creatine tolerance test.¹

In this study we have investigated the comparative value of such determinations as the basal metabolic rate, the creatine tolerance test, and in addition the velocity of blood flow (saccharin method) ² as aids in diagnosis.

Eighty-seven patients studied by us over a two year period were classified in the following groups (tables 1 to 5).

1. Graves' disease
 - (a) Active—11 cases
 - (b) Inactive—6 cases
2. Borderline cases
 - (a) Autonomic imbalance—49 cases
 - (b) Menopause with autonomic imbalance and hypertension—7 cases
3. Allied disorders
 - (a) Essential hypertension—10 cases
 - (b) Non-toxic goiter—6 cases

} 14 patients
(2 had both conditions)

The cases of active Graves' disease had the characteristic symptomatology. Most of them complained of nervousness, palpitation, sweating, emotional and vasomotor instability, and weight loss. The majority had a

* Received for publication February 12, 1938.

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TABLE I
Graves' Disease

Case No.	Sex	Age	Basal Metabolic Rate	Circulation Time in Seconds	CREATINE TOLERANCE TEST				
					Creatine in gm. per 24 hrs.		Creatinine in gm. per 24 hrs.		Retention Per Cent
					Control Day	Creatine Day	Control Day	Creatine Day	
57	M	35	+59 +41 +52 6 ¹	10 ³ ₄	0	.050	.640	.950	95
58	M	52	+37 +31 +20 +10 +28 +13 - 8 +31 +31 +41 +50 +29 +31 + 9 ²	10 12 ³ ₄ 10 ¹ ₂	.185 .075	.210 .365	.880 .800	.750 .390	98 71
59	F	58	+48 +17	11	.145	.775	.670	.615	37
60	F	45	+66 +52 +48 +42 +25 +43 +24	10 ¹ ₂ 9 ³ ₄ 11 ¹ ₄	0 0 .455 0	.190 .210 .905 .305	.740 .570 .365 .805	.945 1.170 .795 .880	81 79 55 69
61	M	25	+47 +51 +41 ² + 9 ²	5 ¹ ₂					
62	F	21	+35 +49 +37 +21 + 8 +50 ² 0 +25	10	.440 .100	.705 .400	.530 .710	.445 .850	74 70
63	F	19	+15 +54 +62 +64 +38 +13 ¹ + 9	6 6 ¹ ₂ 7 ¹ ₂ 7 ¹ ₂	.050 .180 .095	.400 .695 .115	.435 .815 .755	.670 .695 .785	65 48 98
64	F	56	+36 +29 +20	11 11 ¹ ₂	.045	.560	.450	.560	49
65	M	42	+60 +16 +51 +60 +45 ² +15 ² + 4 ¹ + 9	8 ¹ ₂ 10 ¹ ₂	.175 .025 0	1.190 .645 .125	1.150 .970	.970	1
66	F	69	+51 +29 +43 +34 +24 +29 +22 +13 ² +22 +20 + 7 +47 - 4 +23	8 9 ¹ ₂ 8 ¹ ₂ 10 7 ¹ ₂ 8 ¹ ₂	.390 .320 .305 .096	1.885 .390 .340 .380	.755 .700 .765 .720	.765 .665 .790 ³ .710	87 60 93 97 72
67	F	30	+62 +48 +11 +28 +43 +48 +19 ²	7 6 ³ ₄ 7 ¹ ₄	.260	.395	1.060	1.045	86

TABLE I (Continued)
Inactive Graves' Disease
Asymptomatic

68	F	31	-13	15	.130	.420	.790	.830	71
69	F	38	+66 +37 +43 +31 +45 +54 +27 +25 ¹	10 12	0	.175	.920	.975	82
70	F	27	- 4 + 9	10	.055	.210	.775	.675	85
71	F	39	+14	10 ¹ ₂	.050	.815	.975	.895	23
72	F	42	+ 9	12					
73	F	48	+48 +47 -10 + 6 -10 - 6	14 ¹ ₄	0	.055	.900	.850	94

¹ After operation.² After Lugol's solution.

Figures in italics signify tests made while patient was an in-bed patient in the hospital.

definite tremor and tachycardia. A minority had, in addition to the foregoing, exophthalmos, lid lag, or an enlarged thyroid gland. The inactive cases were instances rendered non-toxic by thyroidectomy or roentgen-ray therapy. Four of these cases continued to present symptoms, chiefly of vasomotor and emotional instability (autonomic imbalance).

The complaints of patients comprising the group of autonomic imbalance were referable to the involuntary nervous system. Thus the outstanding

TABLE II
Autonomic Imbalance

Case No.	Sex	Age	Basal Metabolic Rate	Circulation Time in Seconds	CREATINE TOLERANCE TEST				Retention Per Cent
					Creatine in gm. per 24 hrs.		Creatinine in gm. per 24 hrs.		
					Control Day	Creatine Day	Control Day	Creatine Day	
1	M	36	+20 +18 + 2	9 11½ 10½					
2	F	39	+37 +65 -15	8¼ 9½ 9	.135	.415	.670	.605	72
3	F	35		9½	.055	.635	.970	.720	42
4	F	30	+ 4	9½	0	.090	.900	.960	91
5	F	26	-10	8½ 8½ 10¼ 8½	0	.330	.640	.385	67
					.030	.135	.365	.240	89
6	F	46	+38 +15	11½	.160	.730	.800	.970	43
					.230	.330	.860	.900	90
7	F	31	+33¹	9	.265	.330	1.150	.850	94
8	F	36	+11 +43	7½ 7¼ 7¾	.105	.780	.535	.580	33
9	F	29	+42 +13	11½	0	.630	1.270	.930	37
10	M	30	+ 3	11¾	.095	.190	1.845	1.160	91
11	F	45	+ 3	13	0	.360	.500	.530	64
12	F	59	+45 - 2	11	0	.165	.750	.505	83
13	M	36	- 3	17	0	0	1.040	1.280	100
14	F	37	+24 +23 +36	9½ 10 13½	.055	.700	1.275	1.240	36
			+15						
15	F	40	+ 9	12	0	1.125	.955	1.290	87
16	M	35	+22 +42 +23	11 9½ 10¼	.695	1.000	1.270	1.240	70
			+17 +10 + 5		.070	.655	.910	.990	41
			+ 4 + 2 +31	9½	0	.180	1.310	.950	82
			+25 +14		0	.335	1.590	1.850	66
17	F	45	+36 +49 +20	11	.205	1.220	1.120	1.165	75
			+ 5 +31 +11						
18	M	44	+17 + 1	9 8	.285	.340	.940	.785	95
					.180	.190	.835	1.690	99
19	F	44	0	9½ 11	.090	.380	.800	.710	71
20	F	34	+ 6 +28 +57						
			- 5 +20						
21	F	26	+114 +31 +40	8 11 8¾ 9¼	0	.135	.560	.830	86
			+17 +47² + 3²	10² 9² 10²					
			+ 5						
22	F	29	+64 +37 +30	12½	.170	.220	.440	.245	95
			+19 +25 +20		.155	.605	.880	.660	55
			+ 5		0	.170	.880	.680	83
23	F	59	+33 + 2 - 6	10 10 9¾	.595	.935	.895	.945	66
			+ 1		.210	.875	.855	.875	33

TABLE II (Continued)

Case No.	Sex	Age	Basal Metabolic Rate	Circulation Time in Seconds	CREATINE TOLERANCE TEST				Retention Per Cent
					Creatine in gm. per 24 hrs.		Creatinine in gm. per 24 hrs.		
					Control Day	Creatine Day	Control Day	Creatine Day	
24	F	30	+11 -11	8 $\frac{3}{4}$ 10 7 8 $\frac{1}{2}$	0	.150	.790	.620	85
25	F	19	- 3	11 $\frac{1}{2}$	0	.120	.740	.690	88
26	F	31	+46 +30 +35 +21 +54 +23 + 9	8 7 $\frac{1}{2}$ 7 $\frac{1}{2}$ 7 7 7 $\frac{1}{2}$.200 0	.370 .170	1.470 1.130	1.120 1.090	83 83
27	F	33	+22 +38 +15	9 $\frac{1}{4}$ 9 $\frac{1}{4}$.145 0	.445 .280	.836 .870	.810 1.050	70 72
28	F	38	+10	8 9 $\frac{1}{2}$					
29	F	25	+28 +14	8 $\frac{1}{4}$ 8 $\frac{1}{4}$	0	.120	.850	1.060	88
30	F	18	-20 -24	10 $\frac{1}{2}$					
31	F	23	+24 + 5 +15 + 7	13					
32	F	29	+71 +37 +29 + 9	7 $\frac{3}{4}$.060	.495	.750	.825	56
33	F	38	+12	15	.055	.120	1.110	.795	94
34	F	29	+16 +43 + 2	6 $\frac{1}{2}$ 8 $\frac{1}{2}$ 8 $\frac{1}{2}$.040	.080	.740	.980	96
35	F	40	+ 2	13	.070	.420	.620	1.400	65
36	F	74	+41 +30 +16	12	.120 0	.100 .450	.470 1.200	.660 1.200	102 55
37	M	40	+25 +22	13 12					
38	F	28	- 5 +19	12 $\frac{3}{4}$.055	.090	.730	.660	97
39	M	40	+42 + 4	16 $\frac{1}{2}$.135 0	.320 0	1.025 1.450	1.470 1.640	82 100
40	F	37	+23 0	10 13 $\frac{1}{2}$ 13	.165 0	.520 .295	.985 .960	.860 .835	65 70
41	M	43	+21 -16	11 $\frac{1}{4}$ 15	.355	.490	1.415	.730	87
42	F	33	+30 +18 0	10	0	.180	.730	.650	82
43	F	40	+10	8 $\frac{3}{4}$.295	.535	.875	.805	76
					.080	.340	.500	.430	74
44	F	64	+20 +23 +20 +10	15 15 $\frac{1}{2}$.065	.196	.745	.885	87
45	F	33	+30 +45 + 2	9 $\frac{1}{2}$ 9	.130	.400	.830	.600	73
46	F	38	+38 +16	9 $\frac{1}{4}$ 8 $\frac{1}{2}$					
47	F	38	+28 +12 +43	8 $\frac{3}{4}$ 9	.060	.180	.770	1.090	88
48	F	55	+20 +20 0	12	0	0	.850	1.330	100
49	F	42	+21 +16 - 8 +31 +18 +56 - 2	10 $\frac{1}{2}$	0	.365	.625	.475	63

symptoms and signs in these cases were palpitation, dyspnea, tachycardia, tremor, sweating, vasomotor and emotional disturbances, nervousness, anxiety states, episodes of diarrhea, "indigestion," menstrual disturbances, headache and insomnia. Kessel and Hyman³ have clearly delineated this group and applied to it the term "autonomic imbalance." This entity has been referred to by other authors as Graves' constitution,⁴ "forme fruste" of hyperthyroidism, neurocirculatory asthenia, and Basedowoid.

TABLE III
Menopause with Autonomic Imbalance and Hypertension

Case No.	Basal Metabolic Rate	Circulation Time in Seconds	CREATINE TOLERANCE TEST				
			Creatine in gm. per 24 hrs.		Creatinine in gm. per 24 hrs.		Retention Per Cent
			Control Day	Creatine Day	Control Day	Creatine Day	
50	+21 +18 + 5	10 9½ 9 9 9½	0	.365	1.065	1.100	63
51	+ 9 + 5	9½	.055	.410	1.275	1.090	64
52	+15 +35 +61 +12	12	.080	.200	.530	.695	88
53	+16 +41 +13 +48	13 13½	.045	.130	.880	.725	92
	+15 +32 +31 +38						
	+33						
54	+ 9	9	.070	.100	.790	.905	97
55	+35 +26	10½	0	.020	1.050	.720	98
56	+36 - 3 +25 - 5	9½ 10 11	.070	.390	1.250	1.060	68

TABLE IV
Essential Hypertension

Case No.	Sex	Age	Basal Metabolic Rate	Circulation Time in Seconds	CREATINE TOLERANCE TEST				
					Creatine in gm. per 24 hrs.		Creatinine in gm. per 24 hrs.		Retention Per Cent
					Control Day	Creatine Day	Control Day	Creatine Day	
74	F	51	+31 +14	11½ 12 12½					
75	M	15	-28 - 3	10 8½	0	.165	.920	1.025	83
76	M	55	+25 +10 +19	15	0	.280	1.350	1.210	72
77	F	60	+27 +25 +20	11½ 10	0	.205	.925	.990	79
			+24 +12						
78	F	38	+25 - 4	9½					
79	F	48	+31 +14	14	.015	.020	.365	.415	100
80	F	42	+26 +10	8 8½	0	.190	1.055	1.090	81
81	F	41	+24	11					
82	M	53	+ 3	11 13½					
83	F	44	0	10	.050	.100	.920	.635	95

The remainder of the patients had essential hypertension or non-toxic goiter. In general the differential diagnosis from Graves' disease was clear clinically, but sufficient objective or subjective manifestations were present to warrant their inclusion as allied diseases.

The clinical and laboratory findings in Graves' syndrome have repeatedly been reported upon, whereas the more prevalent borderline cases have re-

TABLE V
Non-Toxic Goiter

Case No.	Sex	Age	Basal Metabolic Rate	Circulation Time in Seconds	CREATINE TOLERANCE TEST				
					Creatine in gm. per 24 hrs.		Creatinine in gm. per 24 hrs.		Retention Per Cent
					Control Day	Creatine Day	Control Day	Creatine Day	
77	F	60	+27 +25 +20 +24 +12	11½ 10	0	.205	.925	.990	79
84	F	15	+27 + 6	11¼ 11	0	.275	.890	.665	72
85	F	48	+18	11¾ 11¼	.255	.380	1.670	1.220	87
					.070	.335	1.235	1.000	73
82	M	53	+ 3	11 13¼					
86	F	26	+13 +18	12	.330	.350	.650	.960	98
					.090	.530	.670	.625	56
87	M	18	- 1	16	.070	0	1.360	1.775	107

ceived considerably less attention. The latter form, in our experience, an important group because they are not infrequently subjected to unnecessary thyroidectomy. Especially prominent in this regard are the cases of autonomic imbalance with or without goiter. Because of this such cases constitute the major portion of our series.

The patients were followed chiefly in the out-patient department but where the clinical diagnosis required further investigation or corroboration they were hospitalized for varying periods.

BASAL METABOLIC RATE

As is well known the basal metabolic rate is uniformly elevated in Graves' syndrome and is reduced by the administration of iodine and by subtotal thyroidectomy. Our experience with this determination in the borderline and allied cases would indicate that initial determinations are frequently elevated and misleading because they are not basal, and that at times repeated determinations with insistence on the most favorable conditions, are necessary before obtaining the true basal rate. Especially does this hold in cases of autonomic imbalance. In some instances we have succeeded in obtaining an accurate (normal) figure only after hospitalization. It is readily seen that an elevated figure obtained in a random determination of the basal metabolism in an ambulatory patient is wholly unreliable. It follows also that in cases where clinical judgment dictates against the diagnosis of Graves' disease in spite of an elevation of the basal metabolic rate, one should adhere to the clinical impression until repeated determina-

tions under ambulatory conditions and, if necessary, after hospitalization fail to register a fall to normal.

Because of the cyclic nature of Graves' disease an occasional patient (cases 58, 62, 67) may show a fall in the basal metabolic rate to well within normal limits after hospitalization and bed rest alone. However, the temporary nature of this finding as well as the presence of other characteristic manifestations leaves no doubt as to the diagnosis.

CIRCULATION TIME

According to Blumgart⁵ and others the velocity of blood flow is roughly in direct proportion to the basal metabolic rate. It seemed to us that if the velocity of blood flow mirrored the basal metabolic rate the former determination might be of some value clinically if it were less labile than the latter. The determination of the velocity of blood flow as measured by the saccharin method in terms of arm-to-tongue circulation time has not been used as an adjuvant in the clinical diagnosis of Graves' disease. The circulation time was measured by the interval elapsing between the injection of saccharin into the ante-cubital vein and the perception of the sweet taste in the tongue. By this technic, the arm-to-tongue circulation time in health is between nine and sixteen seconds. One hundred and sixty-seven determinations were made in 88 patients. The resulting data, expressed in average figures and ranges, were tabulated as follows:

	No. of Patients	No. of Tests	Average	Range
1. Graves' disease				
(a) active.	11	27	9½ sec.	5½-11 sec.
(b) inactive.	6	7	12 sec.	10-15 sec.
2. Autonomic imbalance.	48	93	10½ sec.	7½-17 sec.
3. Menopause with autonomic imbalance and hypertension.	7	14	10½ sec.	9-13½ sec.
4. Essential hypertension.	10	16	11½ sec.	9½-15 sec.
5. Non toxic goiter.	6	10	13 sec.	10½-16 sec.

These figures corroborate the previous finding of acceleration of the velocity of blood flow in hyperthyroidism. Thus, the shortest circulation time, 5½ seconds, was obtained in a case of Graves' disease with basal metabolic rates of +47 and +51 determined during hospitalization. Moreover, the range for circulation times in instances of active Graves' disease is distinctly lower than for other cases in this series. However, when the average is taken, the figure is found to be a low normal. On the other hand, the group with inactive Graves' disease (even though symptoms of instability be present) have a normal range and normal average.

From table 2 it is evident that in instances of autonomic imbalance one not infrequently notes a decrease in the circulation time. However, in the

vast majority of cases the velocity of blood flow is normal. The remainder of cases in this series had circulation times within normal limits.

It is readily seen that while, in general, cases with significantly elevated basal metabolic rates have shortened circulation times, it is impossible to use this generalization for diagnostic purposes in specific instances since the differences in the circulatory measurements are not sharply enough drawn and there is considerable overlapping of the ranges. A further diagnostic limitation lies in the observation that a rapid circulation time in Graves' disease may not be significantly altered after relief of symptoms by operation (case 63) or through the taking of iodine (case 66). On occasions, when discordant figures are obtained for the basal metabolic rate and circulation time these figures may be of value. Thus, in a borderline case (case 44) having a considerable elevation of the basal metabolic rate and a circulation time at the upper limit of normal, one can, in the absence of myocardial failure or venous obstruction, entertain the presumption that the figure for the basal metabolic rate is not reliable, and that the case is probably not one of Graves' syndrome.

CREATINE TOLERANCE TEST

Recently there has been introduced a test, by Schorr, based on the previous finding, that patients with Graves' disease have spontaneous creatinuria which disappears on the administration of iodine. This test consists of the administration of creatine by mouth to patients on a creatine-free diet, and the determination of the degree of excretion of this substance. Evidence of a defect in the metabolism is indicated by:

1. Spontaneous creatinuria above 50-60 mg. in 24 hours.
2. Retention of less than 70 per cent of the ingested creatine.
3. Low output of creatine per kilo of body weight.

In another publication⁶ we have analyzed in detail our findings after utilization of this test in the differential diagnosis of the cases forming the basis of this report. Tests were performed on 75 patients. Our protocols indicate that use of this test is sharply curtailed by:

1. The occurrence of partially positive tests, viz., spontaneous creatinuria or decreased tolerance, in control cases.
2. The finding of completely positive tests in some patients with autonomic imbalance.
3. The occurrence of completely positive tests in only 50 per cent of the patients with Graves' disease.

SUMMARY

1. A group of 87 patients comprising 17 cases of Graves' disease and 70 cases of allied conditions (autonomic imbalance, menopause, hypertension

and non-toxic goiter) was studied in an attempt to evaluate the comparative value of laboratory aids such as the basal metabolic rate, the circulation time and the creatine tolerance test in differential diagnosis.

2. In borderline cases, initial and at times repeated determinations of the basal metabolic rate may be elevated and misleading. Repeated determinations are required, after hospitalization if necessary, until they register a fall to normal.

3. The determination of the circulation time fails to afford a laboratory aid in the differential diagnosis between Graves' disease and the borderline cases, since the differences are not clear cut enough and there is considerable overlapping of figures for both groups. Only when discordant figures are obtained for the basal metabolic rate and the circulation time, can these tests be of some suggestive value.

4. Our experience with the creatine tolerance test discloses that it is also limited in its usefulness and may give discordant results.

5. Laboratory aids in general are inadequate as absolute criteria in the differential diagnosis between Graves' syndrome and the borderline cases which simulate it. However, the determination of the basal metabolic rate excels the circulation time test and the creatine tolerance test in usefulness.

It would seem that in the last analysis, clinical judgment surpasses in value any of these laboratory aids. The latter should assume a secondary rôle and be employed with distinct knowledge of their limitations and shortcomings.

We are greatly indebted to Miss Mildred Rosenbluth for valuable assistance in the execution of the tests.

BIBLIOGRAPHY

1. (a) SHORR, E., quoted by RICHARDSON, H. B.: The relation of the thyroid gland to Graves' disease, *Med. Clin. N. Am.*, 1934, xviii, 791.
(b) RICHARDSON, H. B., and SHORR, E.: The creatine metabolism in atypical Graves' disease, *Trans. Assoc. Am. Phys.*, 1935, 1, 156.
2. FISHBERG, A. M., HITZIG, W. M., and KING, F. H.: Measurement of the circulation time with saccharin, *Proc. Soc. Exper. Biol. and Med.*, 1933, xxx, 651.
3. KESSEL, L., and HYMAN, H. T.: Studies of Graves' syndrome and the involuntary nervous system. II. The clinical manifestations of the disturbances of the involuntary nervous system (autonomic imbalance), *Am. Jr. Med. Sci.*, 1923, clxv, 513.
4. MOSHCOWITZ, E.: The nature of Graves' disease, *Arch. Int. Med.*, 1930, xlvj, 610.
5. BLUMGART, H.: The velocity of blood flow in health and disease, *Medicine*, 1930, x, 1.
6. SOHVAL, A. R., KING, F. H., and REINER, M.: The creatine tolerance test in the differential diagnosis of Graves' disease and allied conditions, *Am. Jr. Med. Sci.*, 1938, cxcv, 608.

ELECTROCARDIOGRAPHIC FINDINGS FOLLOWING CAROTID SINUS STIMULATION *

By W. KENDRICK PURKS, M.D., F.A.C.P., *Vicksburg, Mississippi*

It is well recognized that "vagotonia" may have an important bearing upon several cardiac disorders such as auricular premature beats, heart block, and bundle-branch block. It is also accepted that activity of the carotid sinus reflex, among other things, results in increased vagus effect which may at times aid in controlling paroxysmal tachycardia. If the above facts alone did not indicate the desirability of giving much study to the carotid sinus reflex, certainly recent developments would do so. The fact that Weiss¹ and his associates in three years observed 56 patients who suffered from attacks of unconsciousness due to overactivity of the carotid sinus reflex would alone justify widespread interest in the subject. Smith² incidentally has referred to 85 similar cases observed at the Mayo Clinic. For some years Sigler³ had been making careful and comprehensive clinical observations on the carotid sinus reflex but the description by Weiss and associates of a definite syndrome due to abnormality of the reflex has greatly increased interest in its mechanism. This is especially true because the syndrome they describe had to do with loss of consciousness. As Smith has pointed out, "There is hardly a condition in the field of medicine that disturbs the patient or affects his general morale as much as does the loss of consciousness or a severe attack of vertigo." Medical literature contains many reports which show that a variety of unconscious or syncopal spells formerly classed as epilepsy, narcolepsy or simple fainting may in reality be due to overactivity of the carotid sinus reflex.

Also it is becoming more and more apparent that the functions of the autonomic nerve system, which are as yet little understood, have an important bearing upon a variety of functional and emotional disturbances such as chronic fatigue, mental depression, emotional instability, lack of ambition, Raynaud's disease, angina pectoris and various neuroses. Ferris, Capps and Weiss¹ have recently emphasized the relation of the carotid sinus to the autonomic nerve system and suggested that the carotid sinus reflex offers an excellent opportunity to test the action of certain drugs on the central and motor portions of the autonomic nerve system. The possibilities in this field also make it seem worthwhile to study the cardio-inhibitory aspects of the carotid sinus reflex by means of the electrocardiogram.

No attempt is made here to study any except the cardio-inhibitory effects of carotid sinus stimulation by mechanical means. The depressor type of response accompanied by a fall in blood pressure and the cerebral type of response in which syncope may occur without alteration of heart rate or

* Read at the New Orleans meeting of the American College of Physicians, March 28, 1939.

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blood pressure were not studied. In view of the fact that the cardio-inhibitory response is often quite marked following carotid sinus stimulation, it is rather surprising to find so few electrocardiographic studies of this subject. A partial review of the literature during the past ten years showed only one contribution devoted principally to electrocardiographic changes produced by carotid sinus stimulation. Sigler⁴ who had previously made clinical studies of the reflex in 345 individuals reported details of electrocardiographic studies on 50 patients. His study showed the predominant effect to be sino-auricular slowing or standstill and varying degrees of auriculoventricular block. He also observed occasional sinus arrhythmia, ventricular escape and nodal rhythm. Changes in the P-wave were frequent and consisted principally of a decrease in amplitude. Changes in the R-wave, R-T segment and T-wave were rare occurrences. It appeared from his studies that the right carotid sinus reflex had a great effect on the sino-auricular node and the left carotid sinus reflex a greater effect in blocking auriculoventricular conduction. In addition to Sigler's electrocardiographic study of the reflex there have been many reports of electrocardiographic findings in one or several cases^{5, 6} that suffered from carotid sinus syncope. Most of these have shown cardiac standstill or inhibition of ventricles to be the mechanism of the seizures. Weiss and Baker⁷ have made a study of the carotid sinus reflex in 128 normal individuals and evidently carried out electrocardiographic studies on many of them although details of such study were not reported. Likewise Smith made electrocardiographic studies of many of the 85 cases of carotid sinus syncope to which he has referred. In a general way one may conclude that the findings of all observers agree essentially with those of Sigler.

The group on which the present study was made consists of 67 individuals, most of whom either had definite heart disease or were suspected of heart disease. The group also includes 21 individuals, chiefly student nurses who had no disease. In considering the general incidence of response it is important to bear in mind the presence of these young women, for it is well recognized that females and young individuals show a low percentage of response to carotid sinus stimulation. The ages of the entire group varied from 12 years to 69 years with an average of 39.67 years. There were 20 males and 47 females. Each case in the group had a complete clinical study and standard electrocardiograms before carotid pressure was tested. All tests were made with the patient in the recumbent posture since we were not attempting to reproduce a syncopal attack but merely to test the effect of carotid pressure on the cardiac mechanism. The electrocardiograms demonstrating the reflex response were all taken in standard Lead II with carotid pressure applied for approximately twelve seconds. The beginning and end of carotid pressure application was indicated on the tracing by the lead marker. The method of applying pressure was as follows: With the head tilted slightly backward and away from the side to be tested, the sinus was considered located just below the angle of the jaw

at the level of the upper border of the thyroid cartilage. Pressure was made on the carotid artery just above this point in such a fashion as to compress it against the spine.

In studying the tracings before and after carotid pressure a general inspection of the curves and careful comparison of the form of all waves was followed by measurement of the P-R interval, Q R S interval, P-P interval, and R-R interval before and after pressure. The tracings after stimulation of the sinus were all studied in the light of previous standard lead tracings. This is important, for otherwise slight changes in sinus rhythm or rate observed in the curves after carotid pressure would have been interpreted as due to activity of the sinus although many of the same changes were present in the standard tracings. Also, minor alterations in the sino-auricular rate were routinely disregarded and not considered as the result of the mechanical stimulation of the carotid sinus reflex even though we might grant that these changes were mediated through the vagus nerve. Often it appeared that carotid pressure did no more than accentuate a pre-existent sinus arrhythmia. These slight changes were disregarded.

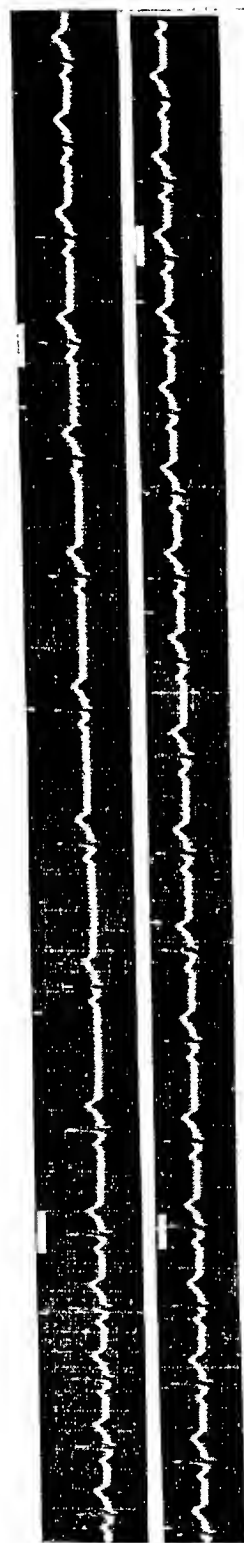
We first present tracings illustrating the various types of responses that were obtained. (See figures 1 to 8.) Each electrocardiogram shown may present evidence of several kinds of change but best typifies one single response. In the complete tabulation of results, of course, all details of each tracing were recorded.

We shall next consider the incidence of each type of response to carotid sinus (table 1) taking up first the most profound alteration in the cardiac

TABLE I
Incidence of Different Types of Response

	Total	Right	Left
Inhibition of ventricle.....	3	1	2
Inhibition of auricle.....	2	2	1
Decreased P-wave.....	12	9	7
Inverted P-wave.....	1	1	0
Prolonged P-R.....	7	5	7
Bundle-branch block.....	1	0	1
Sino-auricular slowing.....	49	38	38

mechanism, namely inhibition of the ventricles. Although the present group of patients contained no individuals who clinically suffered from carotid sinus syncope we were able to induce ventricular standstill in three individuals or 4.4 per cent of those tested. This abnormality was induced once by right carotid pressure and twice by left carotid pressure. Each of the individuals so affected experienced slight dizziness or blurring of vision and would probably have become unconscious if testing had been done in the upright posture.



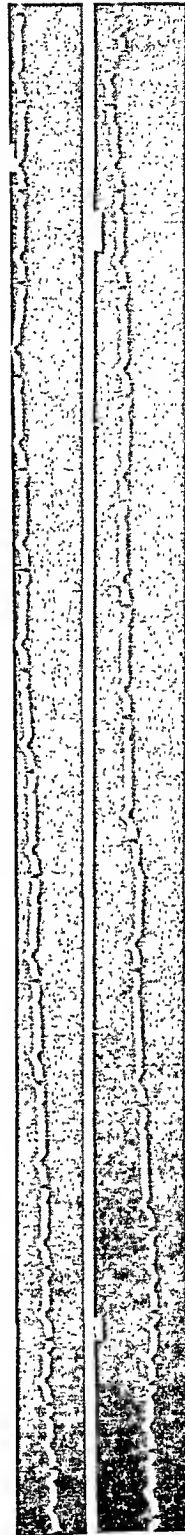
(W.R.P. - CASE 51) ILLUSTRATING SINUS SLOWING (TOP - RIGHT CAROTID PRESSURE)

FIG. 1. Case 51 gives us a good example of sino-auricular slowing best seen here following right carotid pressure. The rate prior to pressure was 86 per minute and at the height of response to the reflex the rate was 42 per minute.



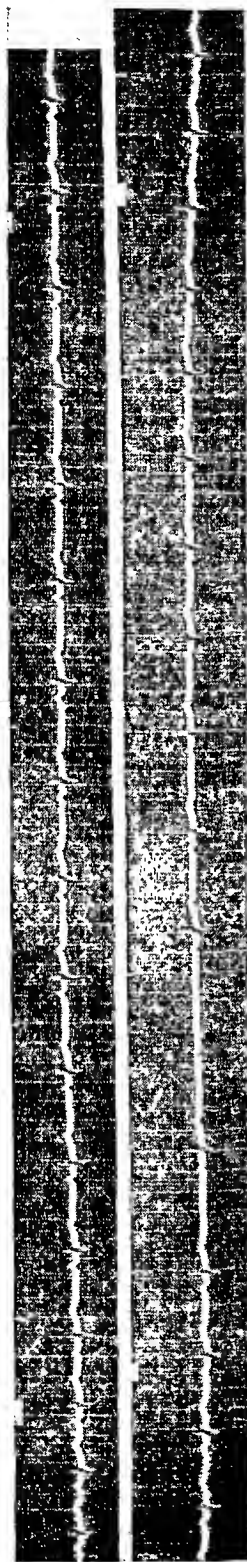
(B.N.K. - CASE 39) ILLUSTRATING INHIBITION OF AURICLES BY RIGHT CAROTID PRESSURE (TOP)

FIG. 2. Case 39 illustrates inhibition of the auricles which persisted for 8.4 seconds following right carotid pressure.



(W.D.W. - CASE 42) ILLUSTRATING PARTIAL HEART BLOCK (P-R INTERVAL 0.25) RIGHT CAROTID PRESSURE ABOVE AND LEFT CAROTID PRESSURE BELOW

FIG. 3. Case 42 shows partial auriculoventricular block with prolongation of the P-R interval to 0.25 second following both right and left carotid pressure.



(L.M.S.-CASE 40) ILLUSTRATING PARTIAL HEART BLOCK (DROPPED BEAT)

FIG. 4. Case 40 also shows partial heart block with dropped beats following stimulation of the left carotid sinus.



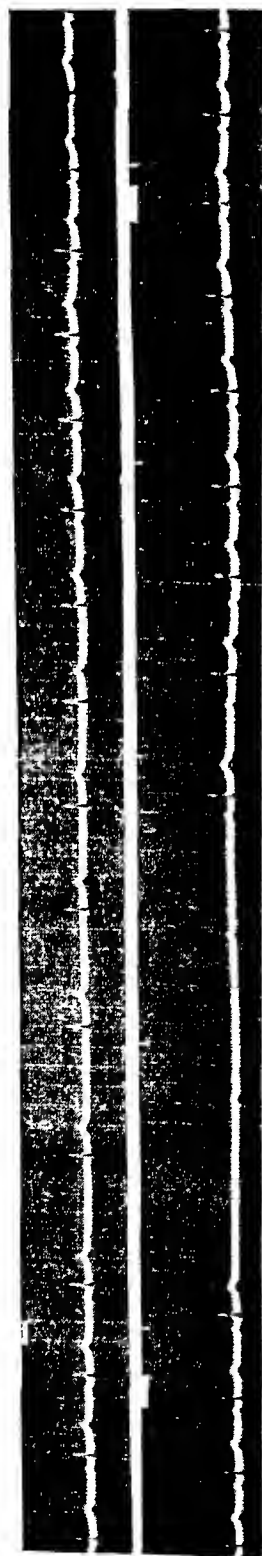
(J.W.N.-CASE 30) ILLUSTRATING DECREASE IN AMPLITUDE OF P-WAVE

FIG. 5. Case 30 presents a typical example of decrease in amplitude of the P-wave. It may be observed following both right and left carotid pressure.



(M.L.A.-CASE 47) ILLUSTRATING INVERSION OF P-WAVE (TOP-RIGHT CAROTID PRESSURE)

FIG. 6. Case 47 shows a displacement of the pacemaker with inversion of the P-wave following right carotid sinus stimulation.



(C. S. - CASE 41) ILLUSTRATING INHIBITION OF VENTRICLE (BOTTOM - LEFT CAROTID PRESSURE)

Fig. 7. Case 41 is an example of inhibition of the ventricles which persisted for 5.4 seconds after left carotid pressure.

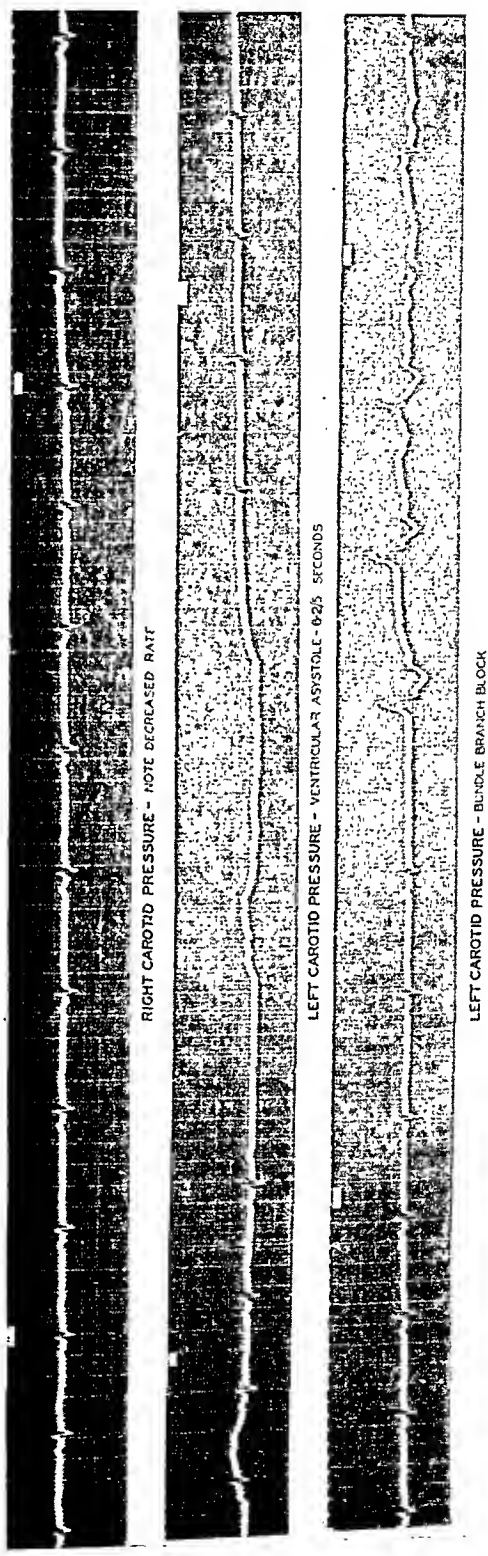


Fig. 8. Case 67 which has previously been reported⁸ shows development of bundle-branch block during stimulation of the left carotid sinus (lower curve). It also shows inhibition of the ventricles for 6.4 seconds (middle curve). In this study no changes were observed in the R-T interval or the T-wave.

Other types of response occurred with the frequency indicated in the table. Inhibition of the auricles appeared three times in two individuals (2.98 per cent), being produced twice by right sided stimulation and once by left sided stimulation. The P-wave showed a decrease in amplitude 16 times in 12 individuals (17.91 per cent), as a result of right carotid pressure nine times and left carotid pressure seven times. There was only one instance of displacement and inversion of the P-wave and it followed right sided stimulation. Various degrees of delayed conduction between auricles and ventricles were found 12 times in seven individuals (10.44 per cent) being the result of right carotid stimulation in five and left carotid stimulation in seven. There was one example of intraventricular conduction disturbance, namely bundle-branch block following left carotid pressure.

By far the most common type of response to both right and left carotid stimulation was sino-auricular slowing. A measurable amount of slowing as judged by P-P intervals before and after stimulation was observed 76 times in 49 individuals (73.13 per cent). Right and left sided stimulation were each responsible for 38 instances of slowing. However, in many of these individuals the amount of slowing was slight and may have been due to factors other than the mechanical stimulation of the carotid sinus by digital pressure. In 27 of the 49 individuals the degree of slowing was considerable and we attributed it to compression of the carotid and so tabulated it in determining the general incidence of response.

We shall next consider the total incidence of effective response to carotid sinus stimulation. Previous reports based principally upon blood pressure and pulse rate changes have shown a high percentage of response, varying from about 60 to 80 per cent. This figure is greatly influenced by a number of factors such as age, sex and blood pressure level. In view of the fact that we are here studying only the cardio-inhibitory aspect of the carotid sinus reflex we cannot assume that the reflex was inactive in all who show negative results here. In the present study definite electrocardiographic changes were induced by carotid pressure in 28 individuals or 41.79 per cent of the total of 67. In most instances in which a response was obtained it was observed after both right and left sided stimulation. There were 24 responses to right carotid pressure and 20 responses to left sided pressure. Males as usual showed a greater incidence of response with definite effects apparent in 14 (70 per cent) of the 20 males tested. On the other hand, only 14 (29.78 per cent) of the 47 females showed a response. We must recall here, however, that 21 of these 47 females were student nurses and therefore much younger as a group than the males. Average age of males was 49.95 years and average of females 34.91 years. If we consider the incidence of response in relation to age alone we find a very striking difference between individuals under 40 years of age and those over 40 years of age. In the former group there were 34 individuals, only five (17.85 per cent) of whom gave a response to carotid sinus stimulation. There were 33 in the older age group and 23 or 82.14 per cent showed a response.

It has previously been observed that the incidence of response to carotid sinus stimulation is increased in the presence of hypertension. If we consider levels of 150 systolic and 90 diastolic as upper limits of normal blood pressure we find that only 14 (29.78 per cent) of the 47 with normal pressure responded whereas of the 20 hypertensive individuals there were responses in 14 or 70 per cent. Again, if we consider only the hypertensive group it is found that seven of the eight males in this group gave a response, that is to say 87.5 per cent as opposed to a response in seven or 58.33 per cent of the 12 females in the hypertensive group. The present group of 67 individuals is too small for us to attach any particular importance to the incidence of response in relation to the disease present. We will, however, list the diagnoses and the number of responses obtained in each.

No disease	21	response 3
Hypertensive and arteriosclerotic heart disease	20	response 14
Cardiac neuroses	4	response 1
Syphilis of heart	1	response 1
Rheumatic heart disease	3	response 1
Congenital heart disease	2	response 0
Miscellaneous	16	response 8

This tabulation does serve to indicate the great frequency of response in the presence of hypertension and arterial disease.

DISCUSSION

The general nature of the electrocardiographic changes induced by carotid pressure in this study bear our previous observations to the effect that carotid sinus stimulation may cause either inhibition of impulse formation in the heart or delay in its transmission through the conduction system. These are features which from experimental and clinical study indicate vagus nerve function. The group of patients here studied is not sufficiently large to indicate a definite difference, if any exists, between right and left sided stimulation. Furthermore it is not strictly correct to suppose that the right and left sinus reflex is comparable to direct stimulation of the vagus nerve. It does, however, appear probable that the reflex on each side is predominantly, at least, manifest through the homolateral vagus and that, just as in the case of animal experimentation with direct stimulation of the vagi, right sided stimulation seems to have a greater influence upon impulse formation in the sino-auricular node and left sided stimulation a greater effect upon auriculo-ventricular conduction and ventricular response. This is suggested by the fact that inhibition of the auricles was twice as common following right carotid pressure, changes in amplitude of the P-wave were nine to seven more frequent after right sided stimulation and the one instance of inversion of the P-wave followed the right sided reflex. On the other hand, there was a seven to five predominance of left sided stimulation in causing prolonged P-R interval, there was a two to one predominance of the left side in causing inhibition of the ventricles and the single instance of intraventricular conduction defect followed the left sided reflex.

The relatively high incidence of profound changes in the cardiac mechanism following carotid sinus stimulation in a group of individuals who had clinically normal carotid sinus reflexes emphasizes the possibility that an overactivity of this reflex may be responsible for syncopal seizures as well as cardiac abnormalities.

The results of the present study coincide with those of previous studies in respect to the influence of age, sex and blood pressure upon the frequency of response to mechanical stimulation of the carotid sinus. Females react less well than males, and the response increases with age and elevation of blood pressure. There has been much discussion in the literature with regard to the causes of overactivity of the carotid sinus reflex. Weiss and Baker⁹ state that it is due to one of three factors: (1) excitability of the afferent nerve endings within the sinus, (2) the state of the medullary centers, or (3) excitability of the efferent cardiovascular nerve endings. Sigler¹⁰ says that all factors point to a constitutional vagotonic tendency. No doubt there are many factors which influence the activity of the reflex, but it appears that the effect of one very obvious factor has received too little attention. This factor proved of importance in this study, and will likewise be of importance in any study of the carotid sinus reflex in which the means of inducing the reflex is compression of the carotid artery distal to the sinus. It is vastly easier to locate and properly compress a carotid artery if that vessel is hardened by arteriosclerosis or distended by hypertension than it is to properly compress a vessel which presents a poor pulsation and is therefore difficult to locate. Previous reports have all left the impression that the actual degree of irritability of the carotid sinus reflex itself was determined by the response obtained from pressure in the neck although a strong response to such "mechanical stimulation" does not of necessity prove an inherent greater tendency to respond, that is to say, nerve irritability, but may be due to a more efficient application of the stimulus in those cases in which the artery is sclerotic or hypertensive. This fact could account for the greater incidence of response in the older age groups and will explain partly, at least, the greater incidence of response in males, for they more often show a hypertension or arteriosclerosis than do females. It must be constantly considered if, as suggested by Weiss and associates, we are to use the carotid sinus reflex as a basis for judging some of the functions of the autonomic nerve system. Also in studying the effect of various drugs in sensitizing or desensitizing the carotid sinus reflex we must remember that in some individuals we may be able to apply more efficient stimulation than in others by reason of changes in the carotid vessel or other structure in the neck. Occasionally the presence of hardened lymph nodes makes mechanical stimulation of the reflex more perfect. It would appear, therefore, that the term "hypersensitivity of the carotid sinus reflex" as applied to those cases that have syncopal seizures might more appropriately be "overactivity or hyperactivity of the carotid sinus reflex" except in those instances in which it may be possible to prove the increased irritability of the

reflex by some means other than mechanical stimulation by pressure in the neck.

BIBLIOGRAPHY

1. FERRIS, E. B., JR., CAPPS, R. B., and WEISS, S.: Relation of the carotid sinus to the autonomic nervous system and the neuroses, *Arch. Neur. and Psych.*, 1937, xxxvii, 365-384.
2. SMITH, H. L.: Fainting attacks resulting from hypersensitive carotid sinus reflexes, *Am. Heart Jr.*, 1937, xiv, 620.
3. SIGLER, L. H.: Clinical observations on the carotid sinus reflex. I. The frequency and the degree of response to carotid sinus pressure under various disease states, *Am. Jr. Med. Sci.*, 1933, clxxxvi, 110.
Idem: Clinical observations on the carotid sinus reflex. II. The response to carotid sinus pressure at various ages and heart rates and rhythms, *Am. Jr. Med. Sci.*, 1933, clxxxvi, 118.
Idem: Clinical observations on the carotid sinus reflex. III. The response to carotid sinus pressure in cases with and without precordial pain, *Am. Jr. Med. Sci.*, 1933, clxxxvi, 125.
4. SIGLER, L. H.: Electrocardiographic observations on the carotid sinus reflex, *Am. Heart Jr.*, 1934, ix, 782.
5. MOSES, H. M., and FEINSTEIN, S. S.: Carotid sinus reflex hypersensitivity, *ANN. INT. MED.*, 1935, viii, 1413.
6. MISSAL, M. E., and CRAIN, R. B.: Alternation phenomena in the electrocardiogram. Occurrence in a patient with active carotid sinus reflex, *Am. Heart Jr.*, 1936, ii, 611.
7. WEISS, S., and BAKER, J. P.: The carotid sinus reflex in health and disease. Its role in the causation of fainting and convulsions, *Medicine*, 1933, xii, 297.
8. PURKS, W. K.: Further evidence in regard to functional bundle branch block, *ANN. INT. MED.*, 1939, xii, 1105.
9. WEISS, S., and BAKER, J. P.: Dizziness, fainting and convulsions due to hypersensitivity of the carotid sinus reflex, *Proc. Soc. Exper. Biol. and Med.*, 1933, xxx, 614.
10. SIGLER, L. H.: Further observations on the carotid sinus reflex, *ANN. INT. MED.*, 1936, ix, 1380.

SUBACUTE BACTERIAL ENDOCARDITIS DUE TO STREPTOCOCCUS VIRIDANS WITH SPECIAL REFERENCE TO PROGNOSIS *

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INTRODUCTION

IN the year 1910 a young man came under my care at St. Luke's Hospital, complaining of daily fever, night sweats, and exhaustion. During the next few days petechiae appeared in crops on the skin, the spleen became palpable, and red blood cells were found in the urine. The presence of a loud systolic murmur over the apex of the heart prompted recourse to blood cultures, whereupon Dr. Rosenow in two attempts succeeded in obtaining an abundant growth of *Streptococcus viridans*. For lack of any specific treatment, this patient was given intravenous injections of sodium cacodylate daily for 12 weeks and was kept in bed. For the first month the fever, petechiae, and hematuria continued without change. During the second month all the symptoms improved. By the end of the third month, the fever was almost normal, embolic signs had disappeared, and the patient was regaining weight and strength. For a year thereafter he led a quiet life, then resumed his business. Today he is in good health, although the heart murmur persists. Because of the unexpected outcome of this case, I decided to make a follow-up study of patients with bacterial endocarditis.

Since then I have attempted to learn the end results of all the patients with *Streptococcus viridans* subacute bacterial endocarditis coming under my observation in private practice and in Cook County and St. Luke's Hospitals. It has been impossible to keep track of most of the Cook County patients after their discharge from the hospital and also a considerable number seen elsewhere.

This paper represents a study of 139 cases of subacute bacterial endocarditis, all followed to the time of death or over a long period of years up to 1937 or 1938.

Realizing that the reliability of blood cultures depends to a degree on skill and experience, practically all cultures were originally made or confirmed by St. Luke's Laboratory.†

By way of introduction, it may be profitable to pass in review the successive milestones marking the progress of our knowledge of bacterial endocarditis from its earliest discovery to our present-day conceptions.

1. *Earliest Recognition.* One of the first descriptions of ulcerative endocarditis was that of Rokitsansky¹ in 1855. He described "fibrinous

* Read at the New Orleans Meeting of the American College of Physicians, March 27, 1939.

† I am indebted to the Borland Fellows of St. Luke's Hospital, especially to Drs. Bargen and Biggs, for their contribution to this study, and to the laboratory directors, Drs. Davis, Dick, and Hirsch.

vegetations on the bicuspid valves in the heart of pneumonia, round and sausage-shaped formations of stiff, hyaline, albuminous matter, enclosing a multitude of small granules, which shrink under the influence of acetic acid." This is one of the earliest descriptions of bacteria in endocarditis. Pasteur² states that as early as 1860 he had seen organisms in chains.

To Virchow,³ 1856, belongs the credit for revealing the relationship of ulcerative endocarditis to infarcts in various parts of the body. Upon these observations Virchow built up his theory of embolism which is rated by pathologists as perhaps his greatest single achievement. He also noticed minute glistening bodies in the endocardial exudate and suggested that if the granules could be brought into etiologic relationship to the endocarditis, the whole process might be explained.

2. *Discovery of Bacteria in Valvular Vegetations.* The conclusive evidence demanded by Virchow was offered by Winge⁴ and Heiberg⁵ in 1869 according to Hektoen.⁶ They demonstrated a heart with "large grayish vegetations on the aortic and tricuspid valves, with ulceration." They found infarctions in the lungs and kidneys. In the endocardial vegetations were "leptothrix chains which were striated like a rosary or string of beads." Probably this is the first convincing description of streptococci in endocardial vegetations.

The association of bacteria with ulcerative endocarditis was further confirmed by Klebs,⁷ 1878, and Köster,⁸ 1886.

3. *Experimental Reproduction of Bacterial Endocarditis in Animals.* At this period the theory of bacterial infection was rapidly gaining adherents, and the influence of Koch was demanding more rigid methods for the proof of this conception.

The experimental method was being introduced, and some investigators turned their attention to the inoculation of animals with pure cultures of the bacteria grown from the ulcerative vegetations of endocarditis. Wysokowitsch,⁹ 1885, occasionally succeeded in producing endocarditis in rabbits in this manner, and he found that more certain results were achieved if the heart valves were previously wounded. Later Rosenow¹⁰ and Kinsella¹¹ perfected the technic to such a degree that they reproduced the endocarditis with ease. Rosenow discovered that the first infections of cocci rarely caused endocarditis, but rendered the animal more susceptible to later inoculations.

4. *Classification of Bacteria.* With the turn of the century, bacteriological studies of the organisms found in the vegetations and in the blood greatly enriched our knowledge of the disease.

It was soon recognized that there were two types of bacterial endocarditis—a primary endocarditis in which the portal of entry was unknown or obscure, and a secondary form of endocarditis in which there was a known source of infection pouring bacteria into the blood stream and producing endocarditis as a part of a general septicemia.

Sittmann,¹² Lenhartz,¹³ and Cannon¹⁴ were pioneers in establishing the value of blood cultures. Lenhartz named the bacteria of ulcerative endocarditis parvus; Schottmüller¹⁵ originated the term *Streptococcus mitior* or *viridans*; Horder¹⁶ called this organism *Streptococcus saprophyticus*; Libman,¹⁷ endocarditis coccus; and Rosenow, a modified pneumococcus. It was later agreed that these were all essentially the same organism, and the term *Streptococcus viridans* was adopted. Other organisms such as the influenza bacillus, pneumococcus, gonococcus, and staphylococcus may be responsible for subacute bacterial endocarditis, but it is the experience of Libman and others that about 95 per cent of all patients with this disease are infected by *Streptococcus viridans*.

5. *Clinical.* Just as in the demonstration of the importance of coronary thrombosis the pathologist showed the way and the clinician slowly learned to diagnose the condition, so in ulcerative endocarditis the pathologist blazed the trail which the clinician followed step by step.

Osler¹⁸ in 1885 first called attention to the acute cases of septic endocarditis and in 1908 he gave a clear description of 10 cases of chronic infectious endocarditis, all with fatal termination. The daily remittent fever, the petechiae, the painful nodes under the skin, the occurrence of emboli in the brain, kidneys, and retina were all noted.

Osler's publication was soon followed by Billings'¹⁹ report of 14 cases of chronic infectious endocarditis, the notable feature of his contribution being the successful blood cultures in every patient—an achievement made possible by repeated efforts and improved technic. In 11 cases Rosenow isolated the "modified pneumococcus," and in three the *Streptococcus viridans*.

Libman then entered the field, and by his extensive pathological, bacteriological, and clinical studies has been a leader in the advancement of our knowledge of the disease.

6. *Healing of Valves.* The first ray of hope for victims of this deadly malady came from Harbitz,²⁰ 1899, and Bartel,²¹ 1901, both of whom expressed their conviction that in the hearts of persons dead from chronic infectious endocarditis some of the lesions were in the "healing" stage and free from bacteria.

In 1912 Libman recorded 11 postmortem cases which showed characteristic lesions of bacterial endocarditis and which during life yielded negative blood cultures. In some instances he could differentiate three stages of the process in valvular vegetations—active bacterial, bacteria-free and healing, and bacteria-free and entirely healed. Clinically the patient with healing valves may develop nephritis or cardiac decompensation, or present a picture similar to that of the patient with bacteremia, i.e., fever, emboli.

Since then LeCount,²² Jaffe,²³ and many other pathologists have borne testimony to the presence of healed lesions in bacterial endocarditis—scarring and calcification with disappearance of bacteria. Hamman²⁴ has

recently emphasized the marked evidence of healing frequently encountered in necropsies.

7. *Clinical Recoveries.* Looking back to this period, it seems surprising that with all the postmortem evidence of healing and healed bacterial endocarditis so little mention was made of clinical recovery. As a matter of fact, the earlier reports of recovery were looked upon with general skepticism.

However, there appears here and there in the literature an isolated report of recovery. Many of these published cases presented unsatisfactory proof of a correct diagnosis; still others, with an adequate clinical history and blood cultures, had survived so short a time that the appearance of recovery might well be interpreted as a remission which so often occurs in this disease.

In the accompanying table (table 1) some of the more authentic cases are cited, along with the treatment administered and the duration of the recovery period.

TABLE I
Reported Recoveries of One Year or More

Author	Year	No. Cases	Treatment	Length of Recovery Period
Latham and Hunt	1910	1	Vaccine	1 year
Oille, Graham and Detweiler	1915	23	Seven with vaccine; others—no therapy	10 years later all living
Lorey	1917	1	Salvarsan	1 year
Salus	1920	18	Not stated	Not stated
Capps	1923	4	Sodium cacodylate	Over 2 years
Hess	1925	1	Kollargol	4 years
Howard	1926	1	No specific therapy	4½ years
Kissling	1935	1	Immuno-transfusion	4 years
Libman	1935	12	No specific therapy	From 3 to 20 years
Kraiss	1936	1	Normal serum	2 years
Horder	1936	2	One with radium; one—immuno-transfusion	18 months to 20 years
Chester	1937	1	No specific therapy	3½ years
Palowe	1939	1	Splenectomy	20 months

There appear in the literature two reports of what might be termed epidemics of subacute bacterial endocarditis.

Salus,²⁸ 1920, describes a group of 18 cases with *Streptococcus viridans* bacteremia, all of notably mild nature, with low fever and leukopenia. At the end of 12 to 18 months most of the patients were living. The scant details presented by the author, however, seriously impair the validity of the diagnosis.

More significant is the report of Oille, Graham, and Detweiler,²⁶ 1915 to 1925. These authors discovered, during a three-year period, a group of 23 persons suffering from mild symptoms of anemia, arthritis, neurasthenia, with little or no fever. All exhibited heart murmurs, and all yielded positive blood cultures of *Streptococcus viridans*. A follow-up report 10 years later revealed that all were living. Because of the reliability of these investiga-

tors, this report stands out conspicuously as the only verified instance of an epidemic of mild or benign subacute bacterial endocarditis.

Thayer³⁷ reports one recovery of unstated duration; he also refers to one case of recovery by Keefer after 7 months, and one by Stengel of unstated duration. Billings had one case of recovery over four years that was never published.

CRITERIA OF DIAGNOSIS

The criteria upon which the diagnosis of subacute bacterial endocarditis is based have been so fully discussed by Coler, Thayer, Blumer,³⁸ and others that it is unnecessary to review in detail all the symptoms and clinical findings of the disease.

At the present time we must depend upon:

1. The signs of an active endocarditis.
2. Fever, often of low grade.
3. Positive blood cultures, revealing either streptococcus, pneumococcus, gonococcus, influenza bacillus, or rarely staphylococcus.
4. Embolic phenomena, viz., petechiae in the skin, red cells or albumin in the urine, enlargement of the spleen, or local symptoms from lodgment of bacteria in the brain, the lungs, or the extremities.

Of all these findings, the heart murmurs and fever are the most constant. Embolic signs may come and go, but without successful blood cultures one cannot be sure of the diagnosis.

We know, however, that many mild cases of subacute bacterial endocarditis escape recognition because of negative blood cultures.

Recently Weiss and Rhoades³⁹ have called attention to a case in which typical necropsy evidence of healed bacterial endocarditis was encountered and whose clinical history and examination had revealed no suggestion of the disease.

INCIDENCE OF SUBACUTE BACTERIAL ENDOCARDITIS OVER LONG PERIODS

The variability of the incidence of this disease year after year is comparable to that seen in other infections.

In the accompanying chart (chart 1) covering the period from 1910 to 1937, I should like to call attention to several deductions:

1. There were very few cases observed in the period from 1910 to 1920.
2. There was an abrupt rise in the number of cases in 1922 (12 cases); a peak in 1923 (22 cases); a fall in 1924 to 13 cases; and an irregular number from 1925 to 1937.
3. The average number of cases from 1922 to 1937 is much greater than in the period from 1910 to 1922.

It is of interest to compare with our series the incidence of subacute bacterial endocarditis in the Massachusetts General Hospital during the period

from 1910 to 1926. From 1910 to 1921 there occurred two to eight cases per annum; in 1922 the number increased to nine; in 1923, to 16; in 1924 it fell to eight; in 1925, to 14; and in 1926 it was down again to seven cases.

The Boston epidemic wave took place in the years 1922, 1923, 1924, and 1925, as compared with the Chicago wave in the years 1922, 1923, and 1924. Morrison ⁴⁰ published at the same time the incidence of rheumatic fever at the same hospital and concluded that it bore no relationship whatever to the incidence of subacute bacterial endocarditis.

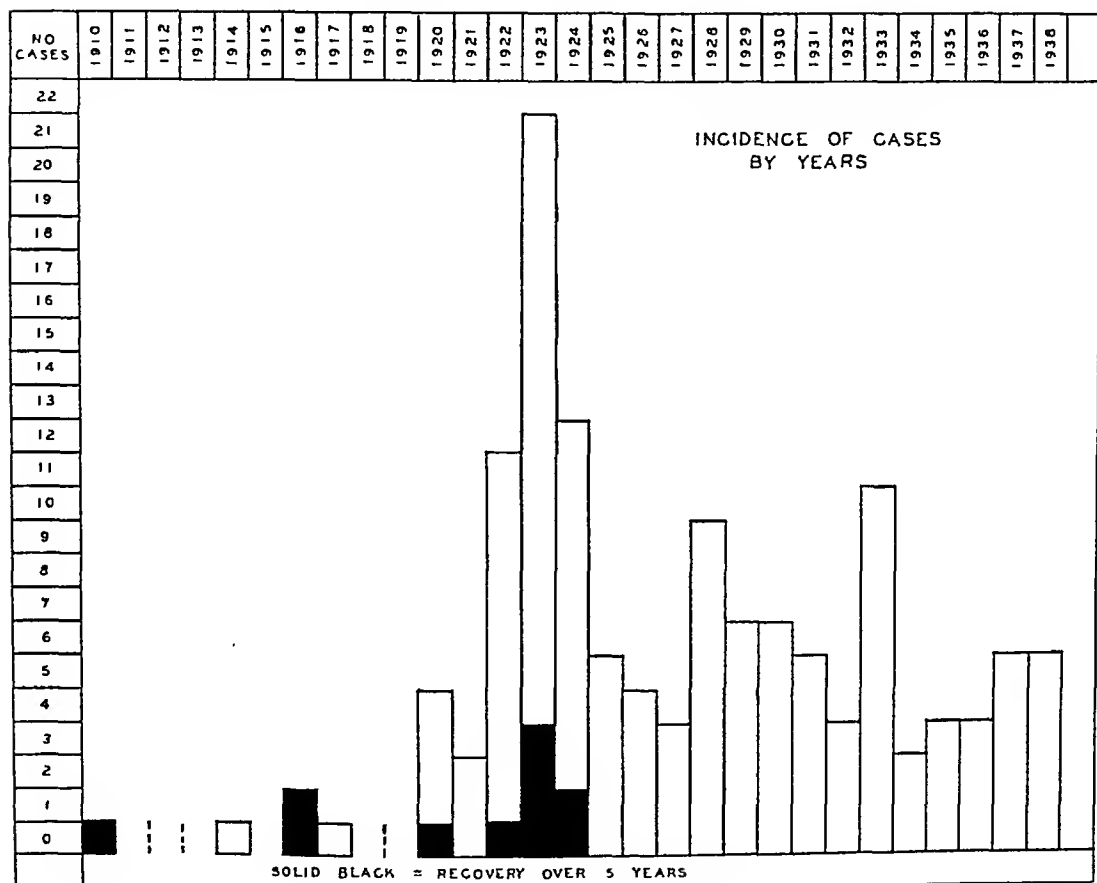


CHART I

4. The recovered cases were observed in the following sequence:

- One in 1910.
- Two in 1916.
- One in 1920.
- One in 1922.
- Four in 1923.
- Two in 1924.

Eight of the 11 cases of recovery occurred in the period from 1920 to 1924.

It has been my misfortune to have seen no instance of recovery since 1924.

ARRESTED OR RECOVERED?

Is the term recovery justified with respect to this disease?

We may profitably compare this infection to pulmonary tuberculosis which is so subject to phases of healing and exacerbation. In tuberculosis the term "arrested" is continually used to designate "improvement." The word "recovered" is reserved for those cases that have gone many years without symptoms.

Likewise, with bacterial endocarditis, we might properly employ the term "arrested" for the cases that are symptom-free. However, a considerable number of patients who become apparently well for months, or even a year or two, undergo a relapse with fresh bacteremia.

In our series of 139 cases there is a group of 10 patients who survived the initial attack one to two years—"arrested cases." Six of this group died from a relapse of the heart infection; four died of cardiac decompensation and nephritis. It has been shown by Baehr that glomerular nephritis is a characteristic sequel of bacterial endocarditis in the bacteria-free stage. Therefore, it might be said that these four nephritic patients died, not from the infection itself, but from its complications.

To avoid any controversy, we have included in this series of recoveries only those patients who have remained symptom-free for a period of over five years.

AUTHOR'S CASES WITH RECOVERY OF FIVE YEARS OR MORE

Eleven patients were living from eight to 26 years after the attack of endocarditis.

Clinically these recovered cases differed from the fatal cases in several respects. Six of the 11 cases were office patients; whereas, the great majority of the fatal cases were confined to bed when first observed.

These patients, with one exception, were not very ill, complaining of weakness, a low daily fever, loss of appetite, palpitation, night sweats, and exhaustion. At first they were suspected of having lymphadenitis, tuberculosis, thyrotoxicosis, or visceral lues, until the appearance of heart murmurs, embolic signs, enlargement of spleen, and positive blood cultures cleared up the diagnosis.

It is noteworthy that seven of the 11 recovered cases occurred in the years 1923 and 1924, corresponding to the peak incidence of all cases.

The only follow-up report of bacterial endocarditis comparable to this series is that of Libman, who describes the recovery of 12 patients for periods ranging from three to 20 years.

A curious circumstance is that nine of Libman's recoveries occurred in the period from 1921 to 1924—the same period in which the majority of

TABLE II
Cases Recovered over Five Years

Name	Date	Period of Observation	Previous Duration	Previous Rheumatism	Valves Affected	Temperature	Emboli				Blood Cultures	Treatment Sod. Cacod.	Outcome
							Spleen	Kidney	Skin	Elsewhere			
1	1910	26 years	1 month	0	M	101 to 102	++	Alb. Rbc.	Petechiae	0	Strep. vir. Twice	10 weeks	Living (1936)
2	1916	19 years	4 months	+	M	97 to 100	0	0	0	0	Strep. vir. Once	4 months	Living (1935)
3	1916	14 years	1 year	0	M-A	99 to 100	+	Alb. Rbc.	Petechiae	0	Strep. vir. Once	9 weeks	Died (1930) De-comp. and Neph.
4	1920	8 years	2 months	+	M	98 to 101	0	Alb. Rbc.	0	0	Strep. vir. Twice	13 weeks	Living (1928)
5	1922	11 years	2 months	+	M	99 to 100.5	0	0	Petechiae	0	Strep. vir. Twice	3 months	Living (1933)
6	1923	14 years	18 months	0	M	97 to 100	0	Alb. Rbc.	0	0	Strep. vir. Twice	3 months	Living (1937)
7	1923	8 years	6 months	+	M	99 to 99.5	0	0	0	0	Strep. vir. Once	3 months	Died (1931) Heart Decomp.
8	1923	9 years	1 month	+	M	98 to 99.5	0	0	0	0	Strep. vir. Once	4 months	Died (1932) De-comp. and Neph.
9	1923	13 years	6 months	+	M	99 to 100	+	0	0	0	Strep. vir. Twice	10 weeks	Living (1936)
10	1924	13 years	2 weeks	0	M	98 to 100	+	0	0	0	Strep. vir. Once	8 months	Living (1937)
11	1924	12 years	9 months	0	M-A	99 to 100	0	Rbc.	0	0	Strep. vir. Twice	4 months	Living (1936)

our cases were seen. Another startling fact is that he records no recoveries since 1924, nor have we observed any since 1924. What is the significance of this coincidence? May we expect to find these cases in clusters like four-leaf clovers? A partial explanation may be that these years represented the peak wave of all cases and in an epidemic wave we may encounter more mild cases. Or must we assume that the organism goes through cycles of changing virulence?

TABLE III
Cases Surviving 5-Year Period

1 patient survived, 26 years, still living.
1 patient survived, 19 years, still living.
2 patients survived, 14 years, one still living, one died of cardiac decompensation and nephritis.
2 patients survived, 13 years, still living.
1 patient survived, 12 years, still living.
1 patient survived, 11 years, still living.
1 patient survived, 9 years, died of cardiac decompensation and nephritis.
2 patients survived, 8 years, one still living, one died of cardiac decompensation

TABLE OF COMPARISON OF RECOVERED AND FATAL CASES

In table 5 is presented a comparison of the recovered with the fatal cases, in respect to the history and the clinical findings.

TABLE IV
Comparison of Recovered with Fatal Cases

	Recovered Cases	Fatal Cases
Previous rheumatism.....	54%	68%
Valves affected { Mitral alone.....	85%	65%
{ Mitral and aortic.....	15%	35%
Temperature.....	99.5° to 101°	101° to 105°
Spleen enlargement.....	35%	75%
Albuminuria or hematuria.....	45%	74%
Petechiae.....	27%	60%
Cerebral embolism.....	0	20%
Osler's nodes.....	0	8%

ENTRY OF INFECTION

It is beyond the scope of this paper to enter into all the discussion pertaining to the origin of subacute bacterial endocarditis, but certain facts have been established which may be enumerated briefly:

1. *Streptococcus viridans* commonly inhabits the throat, tonsils, sinuses, teeth, and intestinal tract, and less frequently the gall-bladder, bronchi, urinary bladder, and genital organs.

2. It is probable that the green streptococci, which have a low degree of virulence, on many occasions enter the blood stream and are destroyed without any resulting damage. However, under certain favoring conditions, the organisms may invade the heart valves—either directly through the coronary arterial capillaries, or more likely by direct implantation on the valves.

3. As in animal experimentation, injury of the valve increases susceptibility to infection; so in human beings, a valve previously damaged by

rheumatism or by a congenital deformity becomes more vulnerable to infection.

PREVENTION

In view of the fact that in a majority of instances the elective location for the invasion of *Streptococcus viridans* is in the site of an old rheumatic endocarditis, our first efforts should be directed to the prevention of rheumatism and rheumatic endocarditis.

We are handicapped in preventing rheumatism because there is no agreement concerning the etiology. However, working on the presumption that it is an infection, valiant efforts have been made to stem the tide of rheumatic fever by eradicating every possible focus of infection that may contaminate the blood stream. So far as may be determined by proved results, the campaign has been thus far disappointing.

More promising are measures proposed for minimizing the damage inflicted on the valves during rheumatic fever, viz., by a prolonged period of rest after the fever has subsided.

It is important to recognize that a patient with an old rheumatic heart valve or a congenital heart lesion is peculiarly vulnerable to *Streptococcus viridans* infection. Therefore, such a person when affected by a respiratory infection should resort to bed rest more promptly and remain in bed a longer time than the average individual.

TREATMENT AND PROGNOSIS

When one peruses the literature of recovered cases and the treatment prescribed, one is impressed with the multiplicity of remedies employed—a circumstance suspicious in itself.

Transfusions of the blood of donors immunized with the patient's organisms have been of doubtful value. Kilgore⁴¹ saw no beneficial effects in three such cases, and in reviewing the reports of Lamb, Howell, Portis, Beverley, Kurtz and White, Wordley, Robinson, and Dick, he concluded that there had been no unequivocal record of success.

Vaccines have failed in extensive tests. Sera of persons immunized against *Streptococcus viridans* have also been of little value, as might be anticipated, since the blood of the victim of subacute bacterial endocarditis is already rich in bactericidal and immune bodies.

Chemotherapy has many votaries: kollargol, mercurochrome, gentian violet, arsphenamine, cacodylate of sodium, and sulphanilamide,—but we cannot pin our faith to any of them. Sulphanilamide has on the whole been disappointing, but it is too early to estimate its value, as several recoveries over short periods have been reported by Hussey⁴² and others.

In all our recovered patients, as well as in most of the fatal ones, sodium cacodylate was given intravenously, three grains a day, over a period of six weeks to three or four months. It is practically non-toxic because of its

rapid elimination. Recent investigations on the action of arsenicals on the spirochete of syphilis and of relapsing fever seem to demonstrate that the chief action of the drug (arsphenamine) is not bactericidal, but that it exerts a powerful stimulus on the reticulo-endothelial system resulting in increased phagocytosis and in the production of immune substances. Therefore, it is conceivable that cacodylate may have some value in this direction.

The most important therapeutic measure, in our opinion, is prolonged bed rest. Many of our recovered patients were ambulatory—not well enough to work, but not ill enough to remain in bed voluntarily. Regardless of their inclination, after the diagnosis was established, these patients were put to bed and kept there for not less than two months, more often for three or four months. Following this rest period, the patient was allowed to exercise very little. The treatment was similar to that recognized as advisable in early febrile tuberculosis of the lung.

To what extent the cacodylate of soda treatment contributed to recovery, it is impossible to say, but probably the drug played a minor rôle.

Do rest and chemotherapy have any value in the ordinary septic case with high fever and numerous embolic phenomena? Very rarely do such patients recover.

Our only hope of a successful outcome is that we may be fortunate in suspecting the condition in certain ambulatory patients who have a low fever of "undetermined origin" and in whom the presence of a heart murmur prompts us to take repeated blood cultures that show colonies of *Streptococcus viridans*. It is in the office and the dispensary, not in the hospital wards, that we will usually discover the mild cases which have some chance of recovery.

I think the time has come for us to change our conventional outlook on this disease. May I again revert to the analogy of coronary thrombosis. For many years the pathologists knew that coronary thrombosis was a common cause of sudden death. At this early period clinicians considered that coronary infarct was nearly always fatal. It was not until Herrick⁴³ taught us how to make the diagnosis during life that we learned that many patients with coronary occlusion survived the attack and even lived many years afterward. Now in the treatment of coronary thrombosis, it is not certain that any remedies materially affect the prognosis, but thanks to early recognition of the infarct the patient is kept in bed over a long period and it is probable that this measure saves a good many lives.

In similar fashion our conception of the prognosis of subacute bacterial endocarditis may change. We have become so familiar with the septic type of the disease, which has nearly always a fatal outcome, that we have overlooked another group of patients with a mild degree of infection in which there is a chance of recovery.

SUMMARY

1. The development of our knowledge of subacute bacterial endocarditis is reviewed. The early recognition of ulcerative endocarditis, as distinct from other forms, was followed by the detection of streptococci in the vegetations. Further studies established the disease as a clinical entity, and blood cultures made possible a classification of the exciting organisms. Pathologists later on described the evidence of healing in the valves before clinical recoveries were reported. In most cases *Streptococcus viridans* is the guilty organism.

2. The more authentic instances of recovery in the literature are cited.

3. The author reports a follow-up of 139 cases of subacute bacterial endocarditis due to *Streptococcus viridans*. These cases were seen in private and hospital practice over a period of 28 years. In all patients there were heart murmurs, fever, blood cultures yielding *Streptococcus viridans*, and often embolic phenomena.

4. A chart recording the occurrence of cases over the period 1910 to 1939 shows a remarkable rise in the incidence of the disease in 1922, a peak in 1923, a recession in 1924, and a smaller average number in succeeding years.

5. The author describes 11 cases of subacute bacterial endocarditis who survived more than five years after the onset of the infection. Eight of these cases occurred in the period 1920 to 1924 when the incidence of the disease was highest.

6. A comparison of the recovered with the fatal cases shows that in the recovered group the fever on the average was lower and embolic phenomena less in evidence. None developed cerebral emboli or Osler's nodes.

7. Clinically the recovered patients with a few exceptions were up and around (complaining of fatigue, palpitation, sweating, loss of appetite, and loss of weight). As a rule they did not seem very ill—in marked contrast to the septic appearance of most of the fatal bed patients. Examination revealed a daily temperature usually around 99° F. to 100.5° F., heart murmurs, and often red cells in the urine, or a palpable spleen. The diagnosis was not determined, however, until blood cultures, often repeated, grew colonies of *Streptococcus viridans*.

8. Treatment of the author's cases consisted primarily of prolonged bed rest of two to four months; also, as a routine, cacodylate of soda was injected intravenously every day for six to 12 weeks. The rest is all important. The value of the arsenic cannot be determined, but at best it plays a secondary rôle.

9. The prospect, with our present knowledge, for improving the chances of recovery in subacute bacterial endocarditis lies, not in treatment of the severe septic cases, but in the early recognition of mild cases and the immediate and prolonged enforcement of bed rest.

10. Finally, it is suggested that a more open-minded attitude may encourage us to investigate more systematically the patients with unexplained

fever and heart murmurs with the hope that early diagnosis and proper treatment will sometimes help nature to arrest the disease.

BIBLIOGRAPHY

1. ROKITANSKY, C.: Lehrbuch der pathologischen Anatomie, ed. 3, 1855, i, 387.
2. PASTEUR, L.: Bull. de l'Acad. de Med., 1879, lxxxix, 256.
3. VIRCHOW, R.: Ges. Abhandl. z. Wissensch. Med., 1856, 705.
4. WINGE, E.: vide Heiberg.
5. HEIBERG, H.: Ein Fall von Endokarditis ulcerosa puerperalis mit Pilzbildungen in Herzen, Virchow's Arch. f. path. Anat. u. Physiol., 1872, lvi, 407.
6. HEKTOEN, L.: The determination of the infectious nature of acute endocarditis, Trans. Chicago Path. Soc., 1930, xiii, 269. (This article contains all the important references on the subject.)
7. KLEBS, E.: Weitere Beiträge zur Entstehungsgeschichte der Endokarditis, Arch. f. exper. Path. u. Pharmacol., 1878, ix, 52.
8. KÖSTER, K.: Die embolische Endokarditis, Virchow's Arch. f. path. Anat. u. Physiol., 1878, lxxii, 257.
9. WYSSOKOWITSCH, W.: Beitrag zur Lehre von der acuten Endokarditis, Centralbl. f. d. med. Wissensch., 1885, xxxiii, 577.
10. ROSENOW, E. C.: Pneumococcus endocarditis, Jr. Infect. Dis., 1909, vi, 245; and 1912, xi, 210.
11. KINSELLA, R. A.: Bacteriologic studies in subacute streptococcus endocarditis, Arch. Int. Med., 1917, xix, 367.
12. SITTMANN, G.: Nebst experimentellen Untersuchungen über die Ausscheidung der Staphylokokken durch Nieren, Deutsch. Arch. f. klin. Med., 1894, liii, 323.
13. LENHARTZ, H.: Über die septische Endokarditis, München. med. Wchnschr., 1901, xlviii, 1123.
14. CANNON, P.: Die Bacteriologie des Blutes, Jena, 1905, 48.
15. SCHOTTMÜLLER, H.: Die Artunterscheidung der für den Menschen pathogenen Streptokokken durch Blutagar, München. med. Wchnschr., 1903, 1, 849.
16. HORDER, T.: Septic endocarditis, Lancet, 1936, ii, 174.
17. LIBMAN, E.: Experiences with blood cultures in bacterial infections, Bull. Johns Hopkins Hosp., 1906, xviii, 215.
- LIBMAN, E.: Lesions of acute bacterial endocarditis, Am. Jr. Med. Sci., 1912, xlv, 313.
18. OSLER, W.: Gulstonian lectures, Lancet, 1885, i, 415.
- OSLER, W.: Chronic infectious endocarditis, Quart. Jr. Med., 1908-1909, ii, 219.
19. BILLINGS, F.: Chronic infectious endocarditis, Arch. Int. Med., 1909, iv, 409.
20. HARBITZ, F.: Studien über Endokarditis, Deutsch. med. Wchnschr., 1899, xxv, 121.
21. BARTEL, J.: Zur Aetiologie u. Histologie der Endocarditis, Wien. klin. Wchnschr., 1901, Nr. 41, 1004.
22. LECOUNT, E. R.: Personal communication.
23. JAFFE, R.: Zur Histologie des Herz Klappen Veränderungen bei der Endocarditis lenta, Virchow's Arch. f. path. Anat. u. Physiol., 1932, ii, 379.
24. HAMMAN, L.: Healed bacterial endocarditis, ANN. INT. MED., 1937, ii, 175.
25. LATHAM, A., and HUNT, E.: A case of malignant endocarditis, Proc. Roy. Soc. Med., 1911, iv, 14.
26. OILLE, J., GRAHAM, D., and DETWEILER, H.: A further report on a series of recovered cases of subacute bacterial endocarditis, Trans. Assoc. Am. Phys., 1924, xxxix, 227.
27. LOREY, A.: Über Endocarditis lenta und die akute, durch den Strep. viridans hervorgerufene Endokarditis, München. med. Wchnschr., 1912, lix, 971.
28. SALUS, G.: Streptococcus viridans bei Endocarditis lenta, Med. Klin., 1920, xvi, 1107.
29. CAPPS, J. A.: The arsenical treatment of chronic infectious endocarditis, Am. Jr. Med. Sci., 1923, clxv, 40.

30. HESS, F. O.: Endocarditis lenta, München. med. Wchnschr., 1925, lxxii, 105.
31. HOWARD, C. P.: quoted by THAYER, loc. cit.
32. KISSLING, K.: Eine auscheinend geheilte Endocarditis lenta, Med. Klin., 1935, xxxi, 1427.
33. LIBMAN, E.: A further report on recovery and recurrence in subacute bacterial endocarditis, Trans. Assoc. Am. Phys., 1933, xlviii, 44.
34. KRAISS, H.: Zur Frage der Ausheilung der Endocarditis lenta, Med. Klin., 1936, xxxii, 566.
35. CHESTER, W.: Patient with ductus botali and endocarditis with recovery, Am. Heart Jr., 1937, xiii, 492.
36. PALOWE, D.: Splenectomy in treatment of proved subacute bacterial endocarditis, Arch. Surg., 1939, xxxviii, 139.
37. THAYER, W. S.: Studies on bacterial endocarditis, Johns Hopkins Hosp. Rep., 1926, xxii, 1.
38. BLUMER, G.: Subacute bacterial endocarditis, Medicine, 1923, ii, 105. (Excellent bibliography up to 1923.)
39. WEISS, S., and RHOADES, C. P.: Bacterial endocarditis, healing and healed, New England Jr. Med., 1928, cxcix, 70.
40. MORRISON, H.: Study of incidence of subacute bacterial endocarditis in Massachusetts General Hospital, Boston Med. Jr., 1927, cxcvii, 46.
41. KILGORE, E.: Subacute streptococcus viridans endocarditis, Am. Heart Jr., 1937, xiii, 619.
42. HUSSEY, H. H.: Probable bacterial endocarditis apparently cured by sulfanilamide, Med. Ann., D. C., 1937, vi, 275.
43. HERRICK, J. B.: Clinical features of sudden obstruction of coronary arteries, Jr. Am. Med. Assoc., 1912, lix, 2015.

THE RÔLE OF THE UPPER SMALL INTESTINE IN THE CONTROL OF GASTRIC SECRETION; THE EFFECT OF NEUTRAL FAT, FATTY ACID, AND SOAPS; THE PHASE OF GASTRIC SECRETION INFLUENCED AND THE RELATIVE IMPORTANCE OF THE PSYCHIC AND CHEMICAL PHASES *

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THE prohibition in Leviticus †: "Ye shall eat no manner of fat, of ox, or of sheep, or of goat," might mean that the ancients were aware of the retardation of gastric digestion by fats. Certainly Aristotle, in his *Problemata*,‡ discussed the effect of fat upon digestion in the stomach with an assurance that indicated much observation and thought.

In 1886 Ewald and Boas ¹ demonstrated that fat in the upper digestive tract decreased gastric activity. Beaumont,² too, had previously stressed the difficulty of digestion of oily foods. From Pavlov's laboratory, however, came the first experiments proving that fat diminished gastric secretion. Khigine,³ who worked on Pavlov pouch dogs, saw a delayed and diminished secretion in the pouch following the introduction of fat into the main stomach. He failed, however, to investigate the mechanism of this action. A short time later Lobassoff ⁴ studied the problem more fully and concluded that fats mixed with meat produced a gastric juice less in quantity and digestive power than that evoked by meat alone. He believed that this action represented a local gastric effect through special nerve endings.

Le Conte ⁵ in 1901, after injecting milk into the duodenum of Pavlov pouch and duodenal fistula dogs, observed an inhibition of gastric secretion. Three years later Sokolov ⁶ almost arrested secretion in the pouch and diminished it greatly in the main stomach of Pavlov pouch dogs by the duodenal instillation of 50 c.c. of cream. Lonnqvist ⁷ in 1906 clearly stated the nature of the mechanism. From studies in the dog, he showed that fat introduced into the stomach and excluded from the intestines exerted no influence upon glandular activity. However, fat instilled directly into the duodenum was followed by a marked suppression of the quantity and activity of the gastric juice secreted. He concluded succinctly: "Fat inhibits gastric secretion.

* Received for publication October 10, 1938.

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† Leviticus 7: 23.

‡ "How," asks Aristotle, "does the stomach come to digest fat meat slowly?" "Because," he answers, "it swims in the stomach. The best digestion takes place at the bottom of the stomach, where the fat does not descend. Those who eat fat meat are sleepy, because their digestion is hindered."

This inhibition is exerted not from the stomach but reflexly from the intestine."*

More recently a number of investigators have confirmed this intestinal action of fat on dogs. However, except for the investigations of Kauders and Porges⁸ and of Roberts,^{9, 10} practically no serious attempts have been made to study this problem in man. We have investigated, in considerable detail, the rôle of the upper small intestine in gastric secretion in the human subject.

In this report, we concern ourselves with the effect upon gastric secretion of neutral fat, fatty acid and soap in the upper intestine; the phase of secretion influenced from the intestine; and the relative importance of the psychic and chemical phases of gastric secretion as indicated by our data.

EXPERIMENTAL METHOD

We selected eight patients with a normal or high gastric acid response to the Ewald meal and with no demonstrable organic gastrointestinal disease. In order to satisfy any questions that might be raised regarding the chemical effect of zweiback and water as the test meal, numerous studies were done with 200 c.c. of a 2 per cent Liebig's extract as the gastric meal. The change in gastric secretion produced by duodenal stimulation was independent of the type of mouth meal used. After an overnight fast, the stomach was intubated with two Rehfuß tubes. One was passed into the duodenum by the usual technic, whereas the other remained in the stomach. When the duodenum was intubated, the positions of the tubes were determined fluoroscopically. The fasting gastric contents were removed and the test meal was administered by mouth. The Ewald meal consisted of 30 grams of zweiback and 300 c.c. of distilled water at body temperature. Duodenal instillation of the test substances in the separate studies was begun with the mouth meal, except when the effect of a time lapse in their administration was being studied.

The effect upon gastric secretion of the additional tube through the pylorus was investigated. We¹¹ have already reported that a tube so placed did not influence gastric emptying; under similar conditions it failed to modify gastric secretion. These results confirmed like reports by Kauders and Porges.⁸ In addition to the duodenal stimulants to be reported here, we studied the effects of hydrochloric acid, organic acids represented by oleic and acetic acid, isotonic and hypertonic solutions of glucose, sodium chloride and sodium bicarbonate, solutions of Liebig's extract, milk and cream, and mineral oil. The duodenal stimulants were instilled from a burette to which a Murphy drip bulb was attached. After the administration of the mouth meal, 15 minute extractions were taken from the stomach in the usual manner for fractional gastric analysis. These extractions were continued in most instances until the stomach was empty.

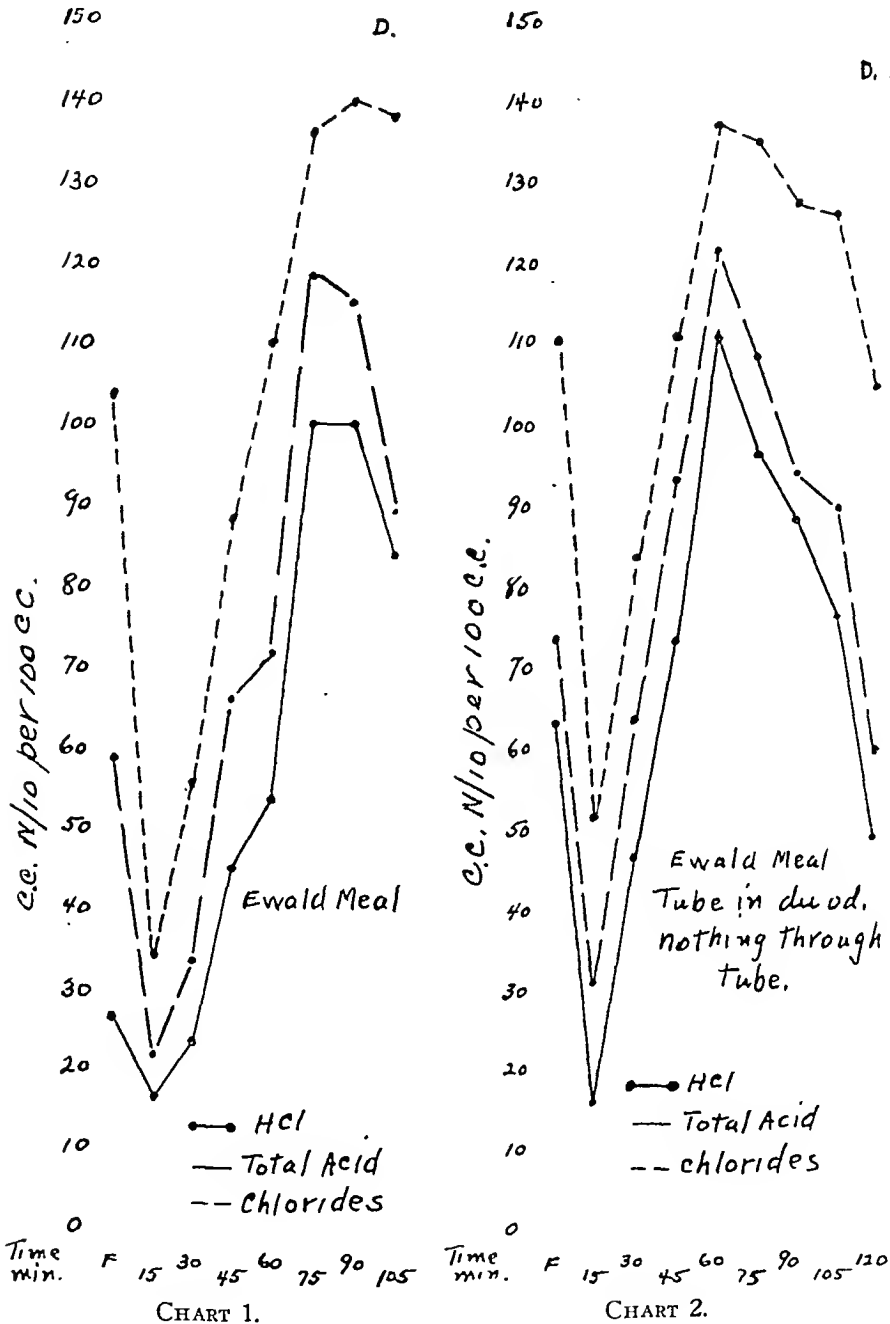
* "Fett hemmt die Magensecretion. Diese Hemmung wird nicht vom Magen sondern vom Darm reflectorisch ausgelöst."

The gastric specimens recovered were titrated for free and total acid by the accepted technic. Total chlorides were determined by the Wilson¹² modification of the Ball method and pepsin was studied quantitatively by a slight modification of the method of Bloomfield and Pollard.¹³

EXPERIMENTAL DATA AND DISCUSSION

Chart 1 shows the curves for free hydrochloric acid, total acid and total chloride in case D, following the Ewald meal alone. Chart 2 is the response in the same individual when the second tube was through the pylorus. No influence upon gastric secretion resulted from presence of the second tube. However, when olive oil was instilled directly into the duodenum at the rate of 40 drops per minute beginning at the time the mouth meal was taken (chart 4), a very marked suppression of gastric secretion resulted (compare chart 3). Total chlorides as well as free and total acid were greatly depressed. At 105 minutes the intraduodenal drip of oil was stopped and the 15 minute extractions from the stomach were continued. Chart 4 shows that this depression in secretion was continued for another 150 minutes when secretion started to rise sharply until 345 minutes, when gastric evacuation was complete. A similar prolonged effect of fat was noted by Sokolov⁹ in his studies in the dog. We have been able repeatedly to duplicate our results. It was interesting to note the almost uniformly depressed level of secretion maintained throughout the test period, giving the impression of a sustained basal secretion by the stomach over which the duodenal mechanism did not appear to have any influence (charts 4, 9). Another feature was the rapid rise in gastric secretion once the inhibited mechanism was freed from the influence of the instilled oil. This rise often equalled the highest levels of secretion seen in the individual. Virschowski,¹⁴ in 1900, was probably the first to observe this secondary rise in dogs. Orbeli¹⁵ reported instances in his dogs in which the secondary rise of secretion surpassed even the usual normal response for the animal. Feng, Hou and Lim¹⁶ using Bickel pouch dogs also saw an exaggerated response in the third hour after olive oil followed by a meat meal. Similar results were reported by Roberts¹⁰ in human subjects.

The possible explanation for the secondary rise in secretion has intrigued most observers. In 1904 Piontkowski,¹⁷ working in Pavlov's laboratory offered the first explanation for this action. He believed that the secondary rise of the secretion of gastric juice was due to the stimulating effect from the products of fat digestion; namely, the soaps. Babkin¹⁸ confirmed this view, having found active gastric secretion in the empty stomach of a dog 15 to 20 minutes after the introduction of a sodium oleate (concentration not stated) solution through a duodenal fistula. Ivy and McIlvain¹⁹ observed similar effects from the application of a 5 per cent solution of ivory soap to the mucosa of intestinal loops in the dog. Practically all observers have accepted the explanation of Piontkowski¹⁷ and Babkin.¹⁸



Patient "D."

CHART 1. Free acid, total acid, and total chloride curve in patient (D) following the test meal alone.

CHART 2. Curves obtained in same patient after similar meal but with a second tube through the pylorus. Note that this second tube did not alter the gastric secretory response to the test meal.

Roberts,¹⁰ although willing to accept their point of view, was not convinced that it was entirely correct. He attempted to clarify the problem by studying the effect upon gastric secretion, after a gruel meal, of the duodenal introduction of an emulsion of linseed oil with sodium oleate. After this procedure, he found a complete suppression of acid secretion for 90 minutes following the gruel meal, followed in turn by a rising curve. His objections to accepting fully Babkin's explanation depended upon the facts:

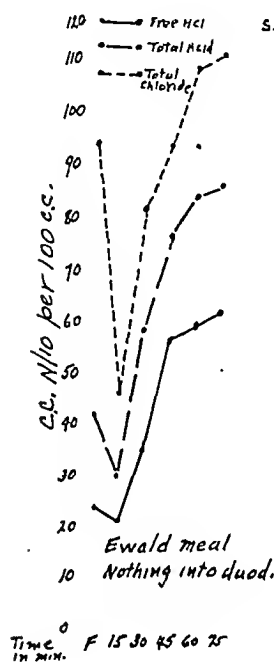


CHART 3.

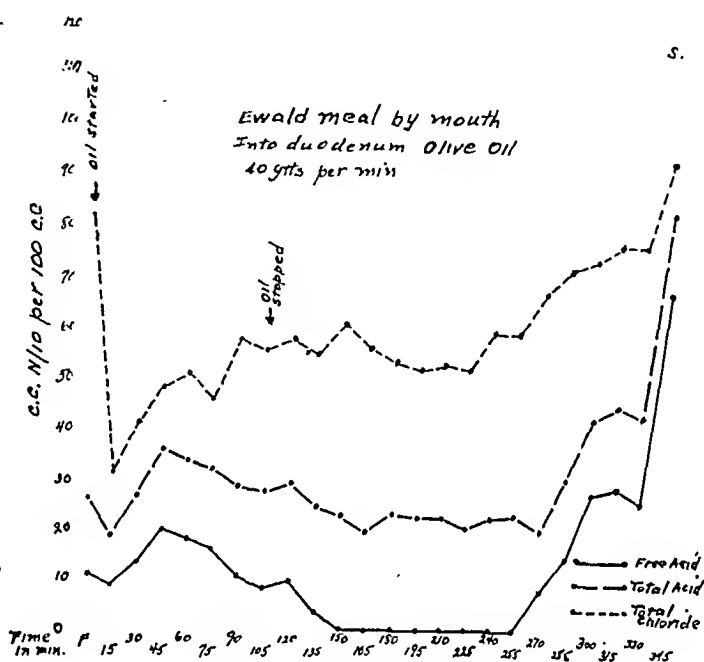


CHART 4.

Patient "S."

CHART 3. Free acid, total acid and total chloride curve in patient (S) following the test meal. The second tube was through the pylorus but nothing was instilled through it at this time.

CHART 4. Conditions same as in chart 3 except that olive oil at the rate of 40 drops per minute was instilled into the duodenum through the second tube. The instillation of the oil was begun when the mouth meal was started, and stopped at 105 minutes later. Note the marked depression in secretion not only of the free and total acid but of the total chloride as well. The depression of secretion was maintained for 150 minutes after the duodenal instillation of the oil was stopped. A sharp rise in gastric secretion then followed which equaled the peak seen in chart 3.

- (1) that the amount of oleate normally present in the duodenum during fat digestion must be very small;
- (2) that the reported effect of soaps was not observed often enough;
- (3) that the inhibitory action of the emulsified oil in his experiments should be seen at once and the supposed oleate effect begin 90 minutes later.

Our own results with sodium oleate solutions justify the misgivings of Roberts¹⁰ and for the human subject at least do not agree with the findings

in the dog of Piontkowski,¹⁷ Babkin,¹⁸ Ivy and McIlvain¹⁹ and others. Chart 5 shows the effect of the duodenal instillation of a 2 per cent solution of sodium oleate. Compared with the result produced with the Ewald meal alone (chart 3), no appreciable effect upon gastric secretion was produced. When, however, the duodenal stimulant was changed to 15 per cent sodium

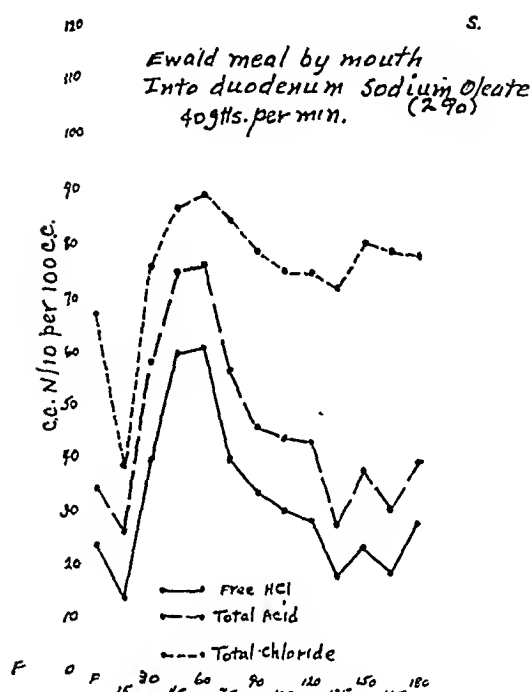


CHART 5.

Instillation of oleate stopped at 105 min.
Patient "S."

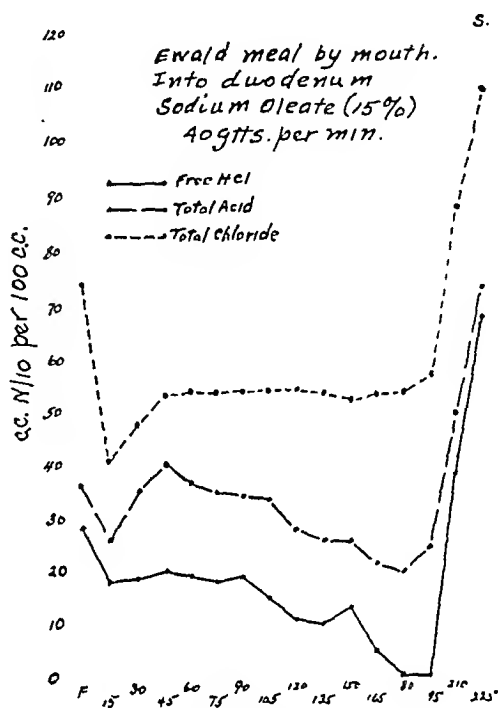


CHART 6.

Instillation of oleate stopped at 105 min.
Patient "S."

CHART 5. Response in patient (S) following the duodenal instillation of a 2 per cent sodium oleate solution under same conditions as in chart 4. Note no appreciable effect on secretion seen as compared with chart 3. However, a very definite delay in gastric emptying resulted. Upon this and chart 6 we postulate a difference in the threshold response of the gastric motor and secretory mechanisms as influenced from the duodenum.

CHART 6. Same as chart 5 except that duodenal instillate was a 15 per cent sodium oleate solution. We now saw a depression of both gastric emptying and secretion, a response entirely comparable in kind to that seen after oil in chart 4. The sharp secondary rise in gastric secretion starting at 195 minutes was also seen. Such results obtained with a soap speaks against the Piontkowski-Babkin explanation that the secondary rise in secretion seen after fat is specifically due to the stimulating effect of soaps formed in the intestine.

oleate, there was a very striking suppression of all the secretory elements (chart 6).

These results permit two rather interesting speculations. First, if we compare the results obtained with the 2 per cent oleate (chart 5) with those of the test meal taken alone (chart 3), we see no appreciable difference in the height of the curves produced, but we do find a very definite delay in gastric emptying in the former. These data indicate that the gastric secretory and motor mechanisms, as influenced from the upper intestine, have

different thresholds of response. The motor mechanism is obviously called into play by a duodenal stimulant milder than the secretory one. However, when the same agent, the oleate solution, is of greater concentration (15 per cent oleate, chart 6) the threshold of response for the secretory mechanism, too, has been passed, which results in secretory, as well as motor, depression. Secondly, the difference between the thresholds of response of the secretory and motor mechanisms, as exemplified in chart 5, probably offers an explanation for the apparent stimulating effect of soaps in dogs reported by

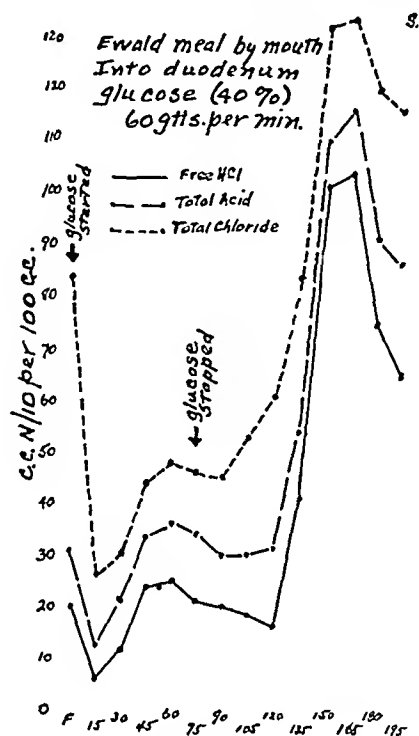


CHART 7.
Patient "S."

CHART 7. Conditions same as in charts 4, 5, and 6, except that duodenal instillate now was a 40 per cent glucose solution. This again showed the depression, followed by the sharp secondary rise in gastric secretion. This rise was most marked after the use of glucose. Such data of course completely negate any specificity to soap as a cause of the secondary rise.

others. If, in their experiments, the soap in the dog's intestine had been of sufficient concentration to inhibit gastric motility but not secretion, such a slowing of gastric emptying could conceivably cause a collection of gastric juice that might falsely indicate an enhanced secretion. Furthermore, chart 6 clearly shows that the action of soap in the intestine in sufficient concentration is identical in kind to that of neutral fat. Finally, any attempt specifically to ascribe the secondary rise in gastric secretion to the presence of soaps in the upper intestine is contradicted by our data obtained with other intestinal stimulants. For present purposes, the results following the duodenal instillation of a hypertonic glucose solution (chart 7) show that no

such specificity exists. Most often, too, the greatest secondary rise in secretion comes after the use of glucose as the intestinal stimulant. We have no explanation to offer for the sharp secondary rise, but we wonder if it might not represent a release of stored up secretion accumulated during the period of depression.

Two factors, other than a specific duodenal mechanism, must be considered to explain the lowered gastric secretion incident to duodenal stimu-

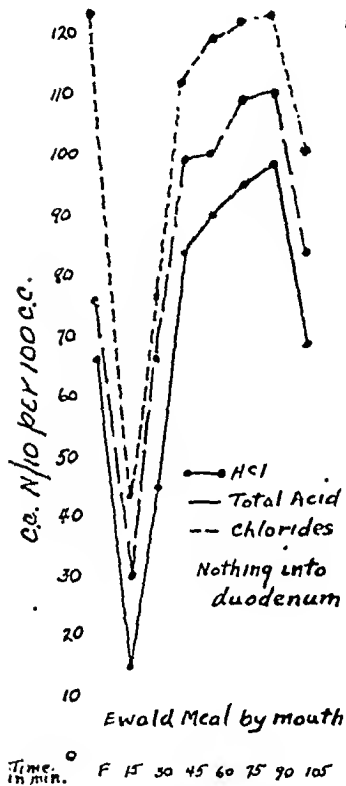


CHART 8.

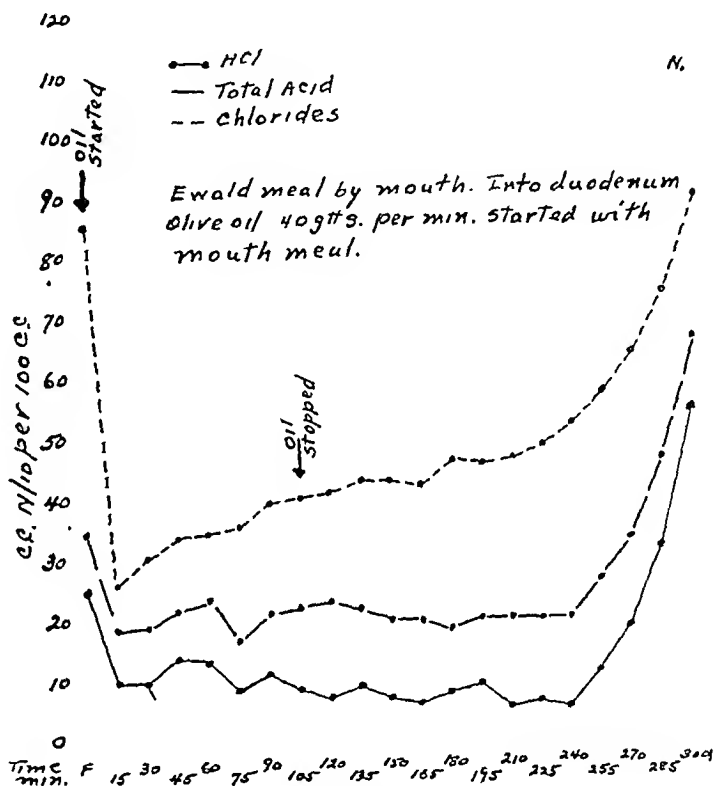


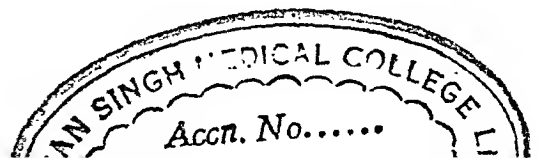
CHART 9.

Patient "N."

CHART 8. Control response to test meal in patient (N).

CHART 9. Response to duodenal instillation of oil in patient N. Conditions same as in chart 4. This chart illustrates very well the question of a basal secretion over which duodenal stimulation appears to have no control.

lation. First, we ¹¹ know from our previous studies on the gastric motor changes from duodenal stimulation, that such stimulation results in delayed gastric emptying. We then have to consider whether the decreased acidity represents merely a dilution of the gastric juice by non-acid diluting fluids from the stomach accumulated incident to the gastric motor delay. Since no reduction in acidity was seen in those instances in which the duodenal stimulant was adequate to produce gastric motor delay without secretory depression, we believe this is not the case.



Secondly, one must consider the possible rôle of duodenal regurgitation in any reduction of gastric acidity in the intact human gastrointestinal tract. Although we²⁰ have shown that the amount of regurgitation is not sig-

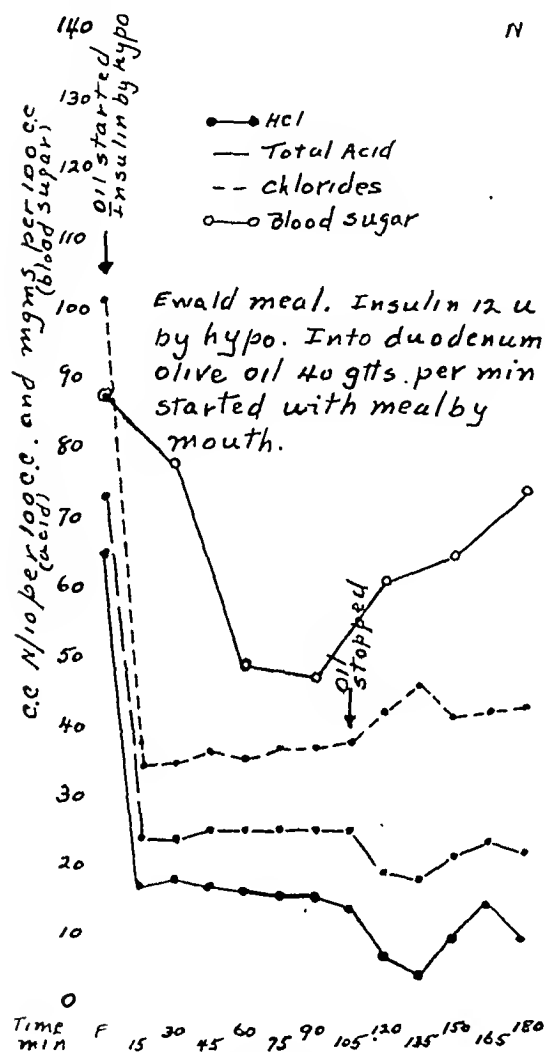


CHART 10.

Patient "N."

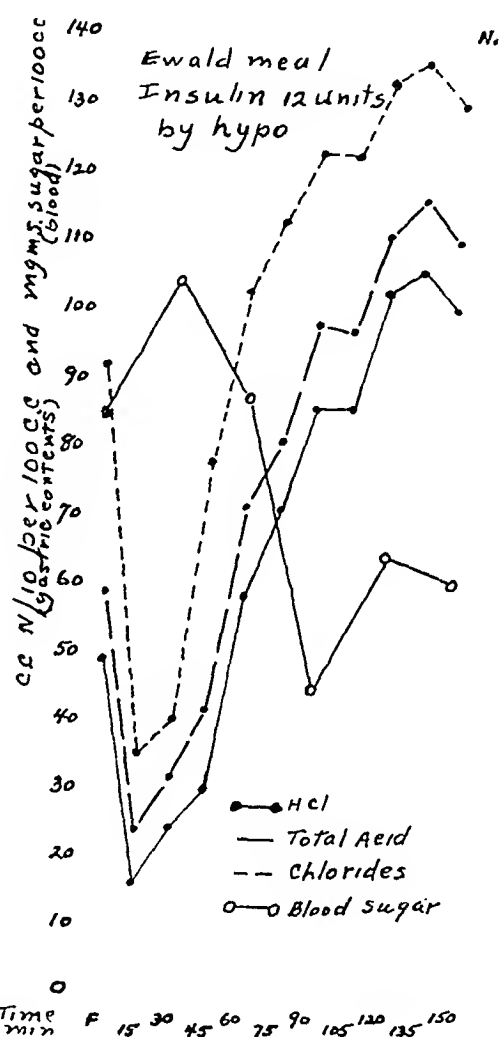


CHART 11.

CHART 10. Conditions same as in chart 11, except that the duodenal instillation of olive oil was started with the beginning of the mouth meal. In spite of the fact that a hypoglycemia as marked as that seen in chart 11 was produced, gastric secretion was almost completely suppressed by the oil in the duodenum.

CHART 11. Blood sugar curve and curves of gastric secretion in patient N after test by mouth and 12 units of insulin by hypodermic given at beginning of mouth meal. Note the increased peak of gastric secretion as well as an increased emptying time that accompanied the insulin hypoglycemia (see chart 8). One does not see a striking increase of acidity over chart 8, since we are dealing with a patient who normally has a high secretory response.

nificant in lowering intragastric acidity in the human stomach (findings adequately confirmed by Maclagan²¹ in clinical studies, by Teorell²² in cats, and most convincingly by Hollander²³ in dogs) the idea of duodenal regurgita-

tion as an important mechanism of gastric acid control is still entertained. We assured ourselves that no regurgitation occurred by using bromsulphalein in our duodenal instillate. This dye, recognizable in alkaline solu-

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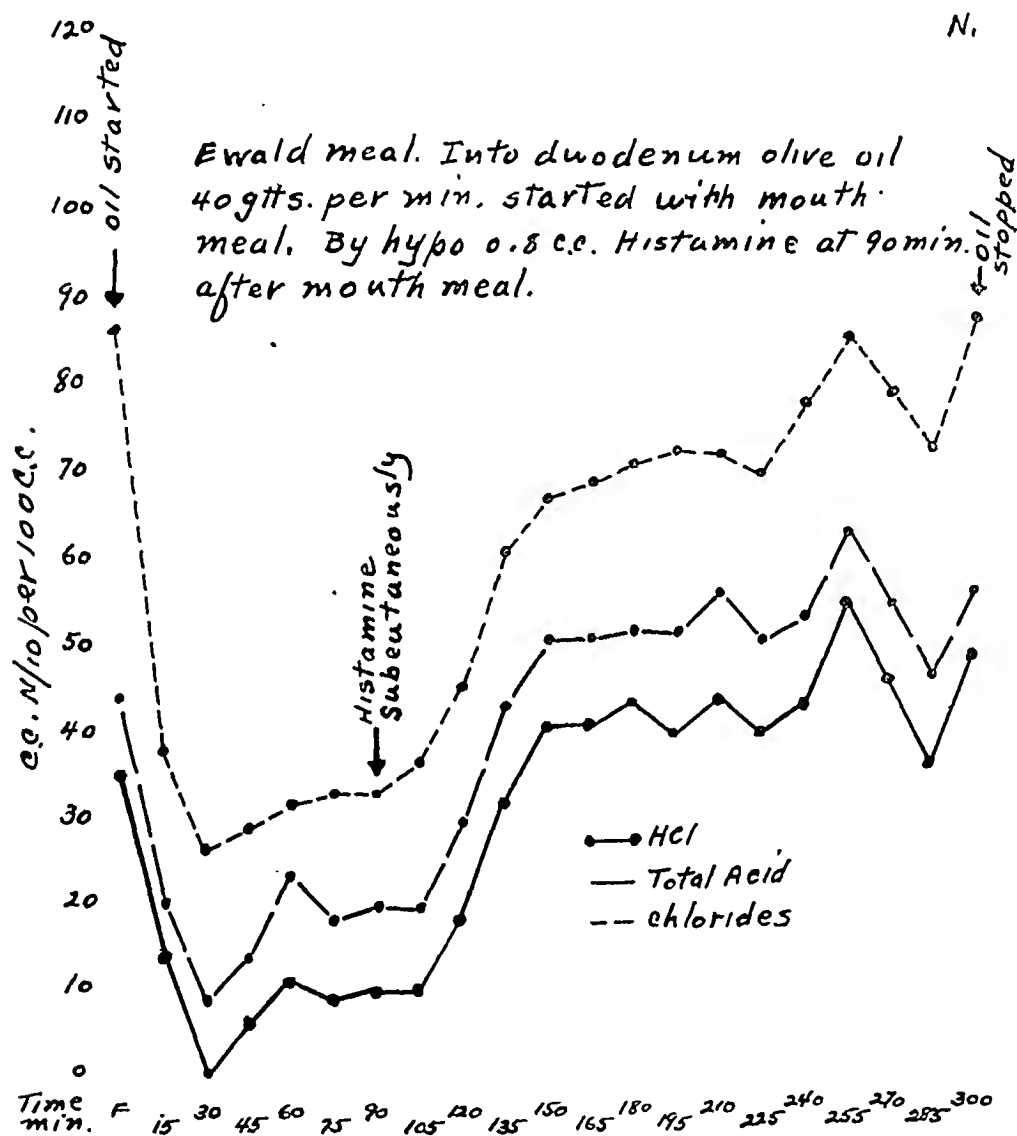


CHART 12. Patient "N."

CHART 12. Olive oil into duodenum started with mouth meal. At 90 minutes when a definite duodenal effect of the oil upon gastric secretion was seen, histamine (0.1 mg. per 10 kilos of body weight) was injected subcutaneously. This was soon followed by a sharp rise in gastric secretion in spite of the fact that the duodenal instillation of the oil was continued for a period of five hours. The results in charts 10 and 12 strengthen the viewpoint that duodenal stimulation influences primarily the cephalic phase of gastric secretion.

tion in one part in a million, was added to the duodenal instillate in amounts approximating 200 milligrams per 100 c.c. A portion of each gastric specimen was made alkaline with 10 per cent sodium hydroxide. Very slight

amounts of duodenal regurgitation could thus be detected easily. Those studies which showed duodenal regurgitation were not included in our data.

We then considered the phase or phases of gastric secretion depressed by duodenal stimulation. Certain of our results led us to believe that the duodenal effect is exerted chiefly, if not entirely, on the psychic phase.

If the rise in gastric secretion incident to the hypoglycemia following insulin injection is dependent upon vagus stimulation, such rise might be considered analogous to that of the psychic phase. Then, if our assumption be correct, duodenal stimulation should prevent the gastric secretory effect of insulin. Charts 8, 10, and 11 show this to be true. In chart 11, we find

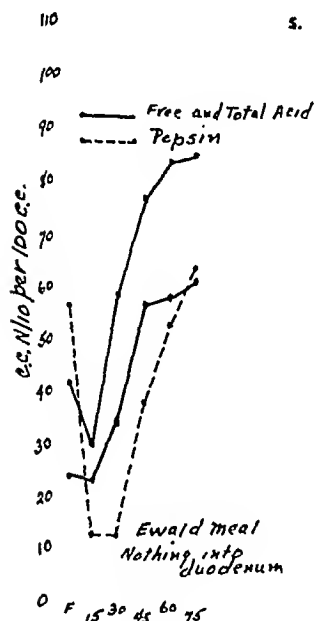


CHART 13.

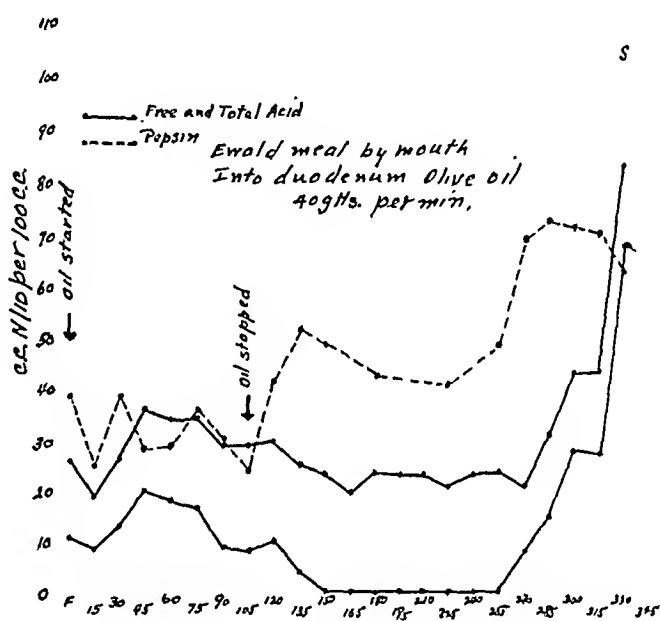


CHART 14.

Patient "S."

CHART 13. Free acid, total acid and pepsin curves in patient S following the test meal.

CHART 14. Same as chart 13 except that olive oil was started into the duodenum with the beginning of the mouth meal. We saw a depression of pepsin concentration as well as that of the other gastric secretory elements. The secondary rise of pepsin secretion appears to take place sooner than does the acid secretion.

the gastric-secretory and blood-sugar curves following twelve units of insulin given at the beginning of the Ewald meal. Chart 10 shows the results following a similar meal and insulin, when the oil was instilled into the duodenum. Although a degree of hypoglycemia similar to that in chart 11 was produced, gastric secretion was maintained only at the basal level seen in chart 9.

Histamine, by its direct effect upon the gastric cell, may possibly be considered to simulate in its action the chemical phase of gastric secretion. Again, if our premise that the cephalic phase of gastric secretion is primarily involved is correct, we should be unable to prevent the gastric secretion called

forth by this agent. Chart 12 illustrates the results obtained. The duodenal instillation of the oil was begun with the mouth meal, and its influence upon the gastric secretion was recorded for 90 minutes in order to assure ourselves that the usual effect of the oil was produced. At this point 0.8 mg. of histamine hydrochloride was injected subcutaneously. Fifteen minutes after this injection, a sharp rise in gastric secretion began, in spite of the continued duodenal instillation of the oil. Thus the opposite results obtained after insulin and histamine fortify the opinion that the effect of duodenal stimulation is largely if not entirely upon the psychic phase of gastric

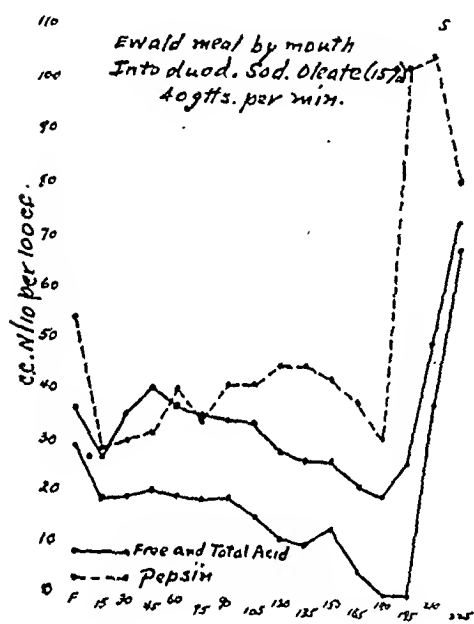


CHART 15.

Patient "S."

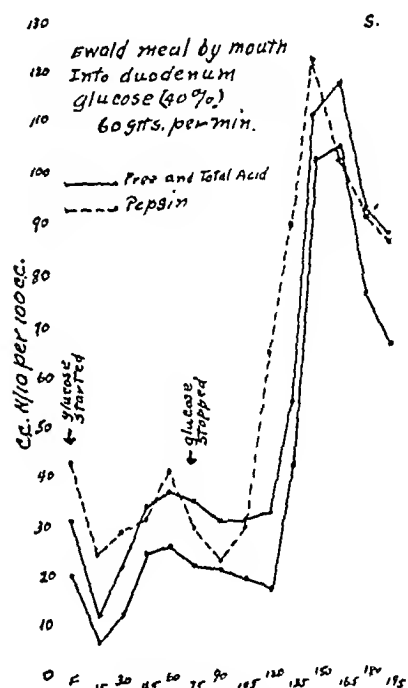


CHART 16.

CHART 15. Conditions same as in chart 14 except that duodenal instillate was a 15 per cent solution of sodium oleate. The sharp rise in pepsin concentration is again seen to just precede the secondary rise in acid concentration.

CHART 16. Shows the same to be true as in chart 14, but now following the duodenal instillation of a 40 per cent glucose solution.

secretion. Such an opinion also finds support in the experiments of Orbeli¹⁵ who found that oil in the duodenum failed to retard gastric secretion in dogs after the vagi were sectioned.

Enzyme secretion paralleled that of the acid and chlorides even to the point of showing the sharp secondary rise following the depression (charts 13, 14, 15, and 16). After the duodenal instillation was stopped, the mechanism of pepsin secretion almost invariably appeared to recover a little before the acid-and-chloride mechanism. This was shown by the earlier secondary rise in pepsin concentration when compared with the acid-and-chloride rise.

SUMMARY

Our studies have shown consistent marked depressions of gastric secretion in man when neutral fats, fatty acids and soaps in proper concentrations were instilled into the duodenum simultaneously with the mouth meal. All secretory fractions were involved: acid, chloride, and enzymes. This depression of secretion continued for a considerable period after the instillation of the stimulant was stopped. A secondary sharp rise in gastric secretion was nearly always observed after the duodenal stimulating effect was overcome. We have not been able to confirm the opinion that this secondary rise in secretion is dependent upon the formation of soaps in the upper intestine, whose action is supposed to cause stimulation of gastric secretion. The duodenal instillation of a representative soap, such as sodium oleate, in proper concentration (15 per cent), has produced, just as oil, first depression then rise in secretion.

We have frequently seen the sharp rise of gastric secretion after the depression stage from agents other than fats. The result obtained with 40 per cent glucose, used to illustrate the action of agents other than fat or fat derivatives, represents the most striking secondary rise of secretion. Obviously, the question of soap formation is not here involved.

By the use of duodenal instillates of different concentrations (2 per cent and 15 per cent sodium oleate), we saw a difference between the thresholds of response of the gastric-motor and secretory mechanisms. The motor mechanism appears to have a lower threshold than the secretory. The mechanism of enzyme secretion also appears to be influenced differently from the acid mechanism. This is seen in the almost consistent earlier rise in enzyme concentration after the duodenal stimulant is stopped.

The question was raised whether the secondary rise in the gastric secretion, following the secretory depression from the duodenal instillation of oil, might not represent a discharge of secretion stored up during the depression period.

We believe that the duodenal influence is exerted chiefly, if not entirely, upon the psychic phase of gastric secretion; and, further, that this phase represents the important one. This is based upon the prevention of the stimulation of gastric secretion during insulin hypoglycemia, and upon the failure of duodenal stimulation to prevent a rise in gastric secretion following histamine injection.

BIBLIOGRAPHY

1. EWALD, C. A., and BOAS, J.: Beiträge zur Physiologie und Pathologie der Verdauung, Arch. Path. u. Anat., 1886, civ, 271.
2. BEAUMONT, W.: Experiments and observations on gastric juice in man, 1883, Plattsburg.
3. KHIGINE, P.: Activité sécrétoire de l'estomac du chien, Arch. d. sci. biol., 1894-1895, iii, 461.
4. LOBASSOFF, J. O.: Sur l'excitabilité sécrétoire spécifique de la muqueuse du canal digestif, Arch. d. sci. biol., 1897, v, 425.

5. LECONTE, P.: Fonctions gastro-intestinales, *La Cellule*, 1900, xvii, 285.
6. SOKOLOV, A.: Analysis of the secretory action of the stomach of the dog, 1904, Thesis, St. Petersburg (In Russian).
7. LONNQVIST, B.: Beiträge zur Kenntnis der Magensaftabsonderung, *Skand. Arch. f. Physiol.*, 1906, xviii, 194.
8. KAUDERS, F., and FORGES, O.: Der Einfluss des Duodenalinhaltes auf die Magensekretion, *Wien. klin. Wchnschr.*, 1922, xxxv, 838.
9. ROBERTS, W. M.: Some observations on the action of belladonna and neutral fats on the acidity of the stomach contents, *Quart. Jr. Med.*, 1925-1926, xix, 74.
10. ROBERTS, W. M.: The effect of oils on gastric secretion and motility, *Quart. Jr. Med.*, 1931, xxiv, 133.
11. SHAY, H., and GERSHON-COHEN, J.: Experimental studies in gastric physiology. II. A study of pyloric control. The rôles of acid and alkali, *Surg., Gynec. and Obst.*, 1934, lviii, 935.
12. WILSON, D. W., and BALL, E. G.: A study of the estimation of chloride in blood and serum, *Jr. Biol. Chem.*, 1928, lxxix, 1.
13. POLLAND, W. S., and BLOOMFIELD, A. L.: A quantitative method for the estimation of pepsin, *Jr. Clin. Invest.*, 1929, vii, 45, 57.
14. VIRSCHOWSKI, A. M.: Du travail des glandes gastriques en rapport avec les différentes espèces d'aliments gras, *Bolnitsch. Gaz. Botkina*, 1900, xi, 1177.
15. ORBELI, L. A.: De l'activité des glandes à pepsine avant et après la section des nerfs pneumogastriques, *Arch. d. sci. biol.*, 1906, xii, 71.
16. FENG, T. P., HOU, H. C., and LIM, R. K. S.: On the mechanism of the inhibition of gastric secretion by fat, *Chinese Jr. Physiol.*, 1929, iii, 371.
17. PRONTKOWSKI, L. F.: De l'action des savons sur le travail des glands à pepsine, *Travaux de la société des médecines russes*, 1904.
18. BABKIN, B. P.: L'influence des savons sur la sécrétion du pancreas, *Arch. d. sci. biol.*, 1905, xi, 209.
19. IVY, A. C., and McILVAIN, G. B.: The excitation of gastric secretion by application of substances to the duodenal and jejunal mucosa, *Am. Jr. Physiol.*, 1923-1924, lxxvii, 124.
20. SHAY, H., KATZ, A. B., and SCHLOSS, E. M.: Experimental studies in gastric physiology. I. Evaluation of the rôle of duodenal regurgitation in the control of gastric acidity in man (Boldyreff Theory), *Arch. Int. Med.*, 1932, l, 605.
21. MACLAGAN, N. F.: Statistical analysis of 389 fractional test meals, with special reference to duodenal regurgitation, *Quart. Jr. Med.*, 1934, iii, 321.
22. TEORELL, T.: Untersuchungen über die Magensaftsekretion, *Skand. Arch. f. Physiol.*, 1933, lxvi, 225.
23. HOLLANDER, F.: Personal communication.

OBSERVATIONS ON THE SPECIFIC TREATMENT (TYPE A ANTISERUM) OF STAPHYLO- COCCAL SEPTICEMIA *

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EARLIER communications from this laboratory ^{1, 2, 3, 4, 5} recorded the partition of staphylococci into two specific groups, which were designated as Types A and B. The differentiation of the types was established primarily by immunological and chemical differences between the intracellular polysaccharides extracted from the respective organisms, and secondarily by the biological distinction that Type A strains are derived from pathogenic conditions, while Type B strains are apparently saprophytic. Other workers ^{6, 7} ^{8, 9} have since confirmed these observations and have, in fact, even discovered additional types among the non-pathogenic strains. ^{6, 9} At a later date, ¹⁰ the determination of types was simplified by the mannite fermentation test, which separates Type A from Type B by the ability of the former to metabolize acid from this sugar. The usefulness of this method, also, has received corroboration from several laboratories. ^{6, 9, 11}

Subsequent investigation on skin reactions ¹² of normal individuals and patients to the carbohydrates of *Staphylococcus* indicated that while the polysaccharide of Type B is cutaneously inert, the similar preparation from Type A elicits reactions in approximately 12 per cent of normal infants and children, and 70 per cent of normal adults. An additional observation of greater importance, however, was that irrespective of skin reactivity, precipitins for the specific carbohydrate were demonstrable in the sera of only those patients suffering from severe, prolonged, generalized infection, and, indeed, only in those eventually recovering from the infection, so that latterly the appearance of precipitating antibodies in the sera of patients has been accepted as a sign of favorable prognosis.

In reflecting upon the significance of the presence of precipitins only in the sera of patients recovering from critical infection, the possible functioning of these antibodies in the mechanism of recovery, perhaps in an anti-invasive capacity, was considered. Accordingly it was proposed to treat patients with staphylococcal septicemia with antiserum containing a high titre of the precipitins capable of reacting with the specific carbohydrates. While conclusive evidence is not yet available to indicate the validity of this hypothesis, i.e., that anticarbohydrate antibodies resist invasion, the results observed with such antisera appear to be of sufficient interest to justify a communication at this time.

* Read at the New Orleans Meeting of the American College of Physicians, March 27, 1939.

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Conducted under a grant from the Commonwealth Fund of New York.

METHODS

Preparation of Antisera. All the antisera utilized in this study have been prepared in rabbits. No special emphasis, however, is laid on rabbit antiserum as possessing any special virtues, since the immunization of rabbits was a matter of convenience and expediency, and it is probable that antiserum from other animals may be equally effective. While still experimenting with methods of serum production, the following is the routine in use at present. Young cultures (18 to 20 hours) grown in veal infusion broth are killed by the addition of 0.2 per cent formalin. Intravenous injections are then made in series of three successive days followed by an intermission of four days. Beginning with a dosage of 0.5 c.c. of culture daily in the first series of injections, the quantity is increased 0.5 c.c. each three-day period until 2.0 c.c. are given. Ten days after the last injection of formalinized cultures, the animals are bled for 50 c.c. or more from the ear vein. The serum from this blood is subsequently processed and reserved for future therapeutic use. Five days later, immunization is resumed with the intravenous administration of living organisms. An injection 0.5 c.c. in volume is given every fifth day, starting with 0.1 c.c. of broth culture diluted to the proper amount, and the dosage is increased each time by 0.1 c.c. of culture. Ten days after the fifth injection (0.5 c.c. of culture), the animals are bled again from the ear vein. The injection of live cultures is repeated as before after five days intermission, and this procedure is conducted as long as the animals tolerate the immunization. It must be admitted that prolonged immunization renders the animals incapable of use, because they become emaciated, the antibody response is greatly reduced, and death frequently intervenes. It does not seem that an ideal method of immunization has yet been attained; several methods have been tried, and while the one described is the best thus far employed and is in use at the present time, improvements are still being sought. Frequent examination made with the sera selected for therapeutic use revealed the absence of so-called antitoxin.

Processing of Antisera. Because of the original toxicity of rabbit serum, an effort has been made at detoxification. For this purpose the method recommended by Goodner, Horsfall, and Dubos,¹³ of adsorption with kaolin and subsequent heating, has been adopted. It has been found that this method requires further improvement, since it is incompletely and irregularly successful.

Administration of Antisera. Because of the widely divergent manifestations accompanying staphylococcal septicemia, it has been difficult to standardize treatment. Each case studied thus far has been a therapeutic problem in itself and has been treated differently from the others. In general, however, 1 c.c. of antiserum in 10 c.c. of saline is injected intravenously as a test dose. If within an hour no significant changes occur in blood pressure (reduction of 15 mm. or more) and respiration (15 beats or more per minute), 50 c.c. of serum diluted in saline may be given intra-

venously, the injection being made slowly, with adrenalin ready for immediate use if indicated. The treatment from then on is based on the clinical signs and the record of blood cultures. Injections may be repeated once or twice daily with 25 or 50 c.c. quantities, and the injections continued as long as the clinical indications demand additional serum. It may be desirable occasionally to continue later administration of serum by giving injections of 15 to 25 c.c. intramuscularly rather than intravenously.

Skin Test to Carbohydrate. In order to measure the adequateness of serum therapy and the development of immunity, use has been made of the skin test to the staphylococcal polysaccharides. This consists of the intracutaneous injection of 0.2 c.c. of a 1:100,000 dilution of Type A carbohydrate, and for purposes of control an equivalent quantity of Type B carbohydrate. The appearance of an immediate wheal and erythema reaction to the Type A carbohydrate alone is interpreted as a sign of immunity, and serum therapy may be discontinued. Whether, however, this test is actually as valuable as it seems to be at the present time requires a much larger number of observations before rendering a final decision. In this study, none of the patients tested¹⁵ reacted when first observed, but, of those recovering, all tested became reactive.

CLINICAL OBSERVATIONS

Up to the time of writing, 17 patients have been treated with antistaphylococcus Type A serum. In each instance the presence of staphylococcal septicemia was established by repeated blood cultures (i.e., at least two) before administration of serum. It is of interest to add at this point that all of the cultures from blood, as well as those isolated from the primary and, in some cases, the secondary foci, were found to ferment mannite and to contain Type A carbohydrate. As was to be expected, the septicemia was always secondary to a primary lesion.

For purposes of more facile presentation, it is desirable to describe the results obtained as observations on patients who survived and those who died.

Synopsis of Patients with Recovery. Of the 17 patients treated with antistaphylococcus Type A serum, seven survived. Of these, three were children with a diagnosis of osteomyelitis as well as bacteremia; two were adults who started with furunculosis and progressed to bacteremia, one even exhibiting clinical signs, verified by the laboratory, of renal abscess; another adult began with an infected blister which advanced into a thrombophlebitis, pyonephritis, cystitis, severe decubitus eventually requiring plastic surgery, and bronchopneumonia; and finally, another adult who, with a primary abscess of the right face, developed bacteremia and bronchopneumonia overnight, the latter condition also due to *Staphylococcus*. These patients received total amounts of serum varying from 75 c.c. to 160 c.c. over periods ranging from five to seven days. In addition to the serum, surgical care

was given wherever indicated, and blood transfusions supplied when necessary.

In making an analysis of these cases, it is obviously difficult to state whether the patients would have survived in the absence of serum therapy, or whether the antiserum was the decisive factor in recovery. Upon retrospection, it is not unlikely that while the antiserum was undoubtedly an adjuvant measure in the three children with osteomyelitis, recovery would probably have occurred despite their severe and critical infection. In the remaining four patients, the infection was particularly acute and critical, so that the physician in charge in each case had begun to concede the case as hopeless. It may well be, therefore, that in these instances Type A antiserum was more than merely adjuvant. It must be admitted, however, that in the ultimate analysis, the evidence on whether survival was the result of the antiserum is inconclusive, just as necessarily must be the case with all contrary-to-fact conditions. If, however, the following observations have any significance: that, in general, bacteremia, measured by colonies per c.c. of blood, was reduced with the first large dose of serum; that the blood usually became sterile within two to four days following commencement of serum therapy; that in those instances when the blood was not immediately sterile, growth of the cultures was retarded to three, four, and five days' incubation, which is in contrast to the usual overnight growth of the cultures before administration of serum, then it would seem that even if a certain degree of doubt regarding the indispensability of the antiserum is entertained, there was with its use definite action on the bacteremia of the patients reviewed above.

The therapeutic effect of the antistaphylococcus serum appears not to be the dramatic, rapid detoxification and defervescence observed with antipneumococcus serum. Recovery is more gradual and the course of the infection still remains prolonged and erratic: thus, in two patients there was a transient bacteremia of one day's duration following periods of sterile blood cultures. The possible reasons for this gradual recovery will be discussed later.

However, no alarming effects were observed in any of the patients during or following the injection of antiserum. In one patient, however, since the preceding injection caused a certain degree of respiratory embarrassment as well as a rash, possible difficulty was avoided by administering the serum mixed with adrenalin. In four of the seven patients surviving the infection, serum sickness was observed. In each individual, this complication appeared in a mild form, consisting of edema and urticaria, and it lasted from one to two days.

Synopsis of Patients with Fatal Infection. The foregoing observations indicate that antistaphylococcus serum, Type A, may confer on the patient a certain measure of benefit by reducing the duration of septicemia and occasionally may even be a deciding factor in survival. With recovery resulting, however, the evidence concerning either its degree of effectiveness or

manner of operation must necessarily be incomplete. Because of the advantage of postmortem observation, on the other hand, it becomes possible to observe in the fatal cases what the influence of the antiserum has been, and how it has affected the infection. In other words, the opportunity is presented to obtain information otherwise available only through direct animal experimentation. Ultimately, all that can be said about surviving patients is that they have survived, while in dying patients what has actually happened may be studied. Fortunately, autopsies were conducted on all the fatal cases, and it is particularly interesting to review the clinical and pathological records of these patients.

As said above, 10 of the 17 patients treated with Type A antiserum eventually succumbed. Four of the patients died within six to 20 hours after serum therapy was begun: of these, two were infants whose original difficulties were feeding problems and in whom the infection appeared to be terminal; the other two, one adult and one infant, were genuine staphylococcal infections. In any case, it is obvious that administration of serum was begun too late in the course of the infection, and indeed they furnish little if any evidence of the potency or impotency of the serum.

In four patients, the blood was sterilized even though death ensued. In one, a boy of 14 years with multiple abscesses, osteomyelitis, and bacteremia, the blood became free of staphylococci after injection of 43 c.c. of antiserum, which was the total supply on hand at the time. After three days during which the blood was found to be free of staphylococci, bacteremia reappeared, and in the absence of further serum treatment the patient progressed rapidly from bad to worse, and at necropsy exhibited all the typical signs of staphylococcal infection (i.e., multiple abscesses of the liver, spleen, kidneys, lungs, heart muscle, and pericardium).

In the remaining three whose blood became sterile following administration of Type A serum, one was a girl of 11 years, who, originally suffering from peritonitis and bacteremia due to Type I pneumococcus, had received prolonged treatment with sulfanilamide which was followed by agranulocytic leukopenia (i.e., for one week the total number of white cells was close to 200, with not a single polymorphonuclear cell to be seen in repeated smears). This condition was quickly followed by Ludwig's angina and staphylococcal septicemia, and her chances of survival under the circumstances appeared extremely poor. A total of 350 c.c. of serum was administered, her blood culture became sterile, and her white blood cell count reached 22,000, with close to 80 per cent of the cells neutrophils. An operation performed on the throat to drain the parotid led to severe and repeated hemorrhages which were not controlled by transfusions and other measures, and the child died within 48 hours. Postmortem examination revealed the astonishing picture of not a single gross abscess in any of the organs or tissue. A blood culture made at the time yielded only hemolytic streptococci, which were considered as terminal invaders of no particular importance. Later, in studying sections, a small, well-organized abscess was located in the lung, much too small

to be within macroscopic visibility. When it is realized that the child ran a course of severe staphylococcal septicemia lasting almost three weeks, it must be admitted that the absence of metastatic abscesses is an extremely unusual picture in this kind of infection.

The second patient entered the hospital with a severe arsphenamine dermatitis with accompanying impaired function of liver and kidney. Perhaps due to the condition of the skin, furunculosis developed and then a bacteremia. The blood became sterile and the patient appeared to be progressing favorably, with specific precipitins demonstrable in the blood, when he died suddenly. Again, postmortem examination revealed no abscess formation in any of the organs, and death was ascribed by the pathologist to arsenic poisoning, since a culture of the heart blood yielded no organisms and the tissue changes justified such a diagnosis.

The last patient of this group, an adult, 58 years old, entered the hospital with a swollen, red, painful wrist and knee, acutely ill and toxic. Blood cultures taken at this time yielded staphylococci. In a few days there was suppuration of the scrotum from which staphylococci were recovered. Within two days 90 c.c. of serum were administered, which appeared to be sufficient to sterilize the blood. Two days later, the patient gave signs of lobar pneumonia, and he died on the following day. At autopsy, absence of abscesses was again noted. The lungs showed typical lobar pneumonia. Cultures taken of the heart blood were sterile, while from the lungs pneumococcus, Type VIII, was isolated.

The remaining two of the patients who died showed typical signs of staphylococcal infection at necropsy. One, a small boy, 1½ years old, had obviously progressed to a point beyond help. There had been suppuration and erosion through the heart wall causing a hemorrhage into the pericardial sac. The hemorrhage was of sufficient duration, moreover, to have become organized and was adherent to both the pericardial and heart wall, and in the resulting blood clot were grossly visible many colonies of staphylococci. Osteomyelitis of the right tibia had become so advanced that the bone was literally floating in pus. It was the opinion of the pathologist that the appearance of the blood clot suggested its antecedence over the administration of serum.

The last patient, an adult of 60 years, from an infected pimple on the nose, progressed to a bronchopneumonia, septicemia, and nephritis. After three weeks' treatment, first with sulfanilamide, then with 100,000 units of antitoxin a day for 10 days, and transfusions every other day, he showed no improvement. He was given 200 c.c. of Type A antiserum without avail. While the septicemia had been reduced during the treatment, it was not suppressed completely. At autopsy, the multiple abscesses in the various organs (liver, kidney, lung, and heart) were typical of the infection.

Thus, then, it is seen that of the 10 patients who died, four were so far advanced as to last less than one day; four had had their blood sterilized, one becoming septicemic again after discontinuance of serum as described

above, while the other three died without the characteristic picture of staphylococcal infection, one of exsanguination, one of arsenic poisoning, and one of pneumonia due to pneumococcus Type VIII. The remaining two died of typical staphylococcal infection, but it is quite likely that serum therapy was begun too late in the progress of the disease. In any case, these are the only cases that can logically be considered as possible failures of the antiserum.

DISCUSSION

Preliminary to an appraisal of the data assembled in this report, it is desirable to point out the cardinal characteristics of severe staphylococcal infection. It is common knowledge that while the large majority of staphylococcal manifestations are usually of minor significance, the possibility is always present of the infection extending into a spreading lymphangitis which may reach the regional lymph glands and may eventually even burst through the tissue barriers into the blood stream. As a localized abscess, however, the condition usually terminates with healing, despite its tendency to persistent recurrences, ultimately its importance being a passing one. Septicemia, on the contrary, is a serious and severe complication; secondary to a local lesion, it incites in the various tissues and organs metastatic abscesses which in turn discharge into the blood stream, thus creating a vicious cycle soon beyond medical and surgical control. Consequently, if any treatment based on specific antiserum is to be effective, it must eliminate or reduce considerably the conditions which promote septicemia; it must check septicemia when present; and it must prevent the formation of metastatic foci. Furthermore, it is necessary to supplement serum therapy with surgical drainage, thus allowing the abscesses to discharge outward rather than into the blood stream. Moreover, if septicemia has been prolonged before antiserum is administered, it is obvious that multiple abscesses may have already been formed in various parts of the body, with the result that, depending upon the extensiveness of the dissemination, both the resistance of the individual and the protective capacity of the serum are completely overwhelmed and death ensues. (Cf. last two patients of second synopsis.)

In contrast to the invasive element of staphylococcal infection briefly reviewed in the preceding paragraph, consideration must be given to the toxic factors as well. During the infection there is a great amount of tissue destruction causing the liberation of toxic substances, which are absorbed to a greater or less extent. In addition, there are metabolic products of growth elaborated by the staphylococcus which are also toxic and also absorbed by the tissues. It is a difficult matter for any variety of antiserum to neutralize all these substances, as is borne out by the use of current antitoxic sera.¹⁴ It is similarly difficult to prevent entirely absorption of the toxic materials by surgical drainage. Consequently, even when septicemia is suppressed completely, the patient inevitably remains toxic and continues in this condition until the various foci have healed. It is small wonder, then,

that even in surviving patients, the course of recovery is apt to be turbulent and prolonged.

It would seem, therefore, that in any form of treatment the most important factor is the prevention or elimination of septicemia. Localized infections are managed successfully by the patient, and the toxicity of the discharging material (bacterial and tissue) is too diversified to allow complete specific neutralization. It was consequently proposed in beginning this study to learn if possible the conditions operating in opposition to the invasiveness of *Staphylococcus*.

The facts outlined in the present report are that rabbit antiserum was prepared to contain antibodies that react with the carbohydrate characteristic of *Staphylococcus*, Type A; this antiserum was used in the treatment of 17 patients with staphylococcal septicemia secondary to a primary lesion; seven patients survived, while 10 died; of those dying, four were started on treatment too late in the disease; one died after checking the septicemia, but treatment was insufficient because the supply of serum became exhausted; three died of other causes after sterilization of the blood, as verified by post-mortem examination; and two, whose treatment was delayed, possibly beyond help, died of typical staphylococcal infection; of the 17 patients, therefore, septicemia was eradicated successfully in 11. If, however, allowance is made for the patients who died in less than 24 hours after inception of serum treatment, the analysis indicates the antiserum was successful in 11 of 13 trials.

It seems, therefore, that under certain conditions, the experimental Type A antiserum employed in this study may be of value in checking septicemia and even in preventing the formation of metastatic abscesses. The antiserum was unable to eliminate the toxemia observed in all the patients, and whether reinforcement with antitoxin will broaden its usefulness is a problem for future study. In any case, it seems wise to supplement the antiserum with supportive measures, particularly surgical drainage and blood transfusions. It is realized that the total number of patients treated thus far form too small a group to allow any conclusions. All that can be said at the present time is that the results observed with this antiserum are encouraging and perhaps hopeful.

SUMMARY AND CONCLUSIONS

1. Seventeen patients suffering with staphylococcal septicemia secondary to a primary lesion yielded on culture staphylococci belonging to Type A and capable of fermenting mannite.
2. All the patients were treated with Type A antiserum prepared in rabbits and were given in addition whatever supplementary measures were indicated (e.g., surgical drainage, blood transfusions, etc.).
3. The untoward reactions ascribable to the serum were mild, and in four patients the treatment was followed by serum sickness.
4. The skin reaction to the carbohydrate of Type A is suggested as an index of sufficient treatment.

5. Of the 17 patients treated with Type A antiserum, seven recovered and 10 died.

6. Of the 10 patients dying, four died before the end of the first day of treatment, four had developed sterile blood cultures (and of these, three died of other causes) and two died with typical signs of staphylococcal infection.

7. Exclusive of the four patients who succumbed within the first day, then, Type A antiserum apparently sterilized the blood in 11 of 13 patients.

The writer acknowledges with appreciation and gratitude the assistance of the following physicians for both referring the patients and assuming their complete care and responsibility:

Dr. Alexis F. Hartmann, Children's Hospital, St. Louis.....	seven patients
Dr. David P. Barr, Barnes Hospital, St. Louis	three patients
Dr. Thomas P. Findley, Jr., City Hospital, St. Louis	one patient
Dr. Joseph C. Jaudon, Children's Hospital, St. Louis	one patient
Dr. Park J. White, Children's Hospital, St. Louis	one patient
Dr. Joseph C. Edwards, City Hospital, St. Louis	one patient
Dr. Walter J. Siebert, DePaul Hospital, St. Louis	one patient
Dr. J. G. Probststein, Jewish Hospital, St. Louis	one patient
Dr. Paul F. Stookey, St. Mary's Hospital, Kansas City, Mo.	one patient

REFERENCES

- JULIANELLE, L. A., and WIEGHARD, C. W.: Immunological specificity of carbohydrates derived from *Staphylococcus*, *Proc. Soc. Exper. Biol. and Med.*, 1934, xxxi, 947-949.
- JULIANELLE, L. A., and WIEGHARD, C. W.: The immunological specificity of staphylococci. I. The occurrence of serological types, *Jr. Exper. Med.*, 1935, lxii, 11-21.
- JULIANELLE, L. A., and WIEGHARD, C. W.: The immunological specificity of staphylococci. II. The chemical nature of the soluble specific substances, *ibid.*, 1935, lxii, 23-30.
- JULIANELLE, L. A., and WIEGHARD, C. W.: The immunological specificity of staphylococci. III. Interrelationships of cell constituents, *ibid.*, 1935, lxii, 31-37.
- JULIANELLE, L. A., JONES, D., and HARTMANN, A. F.: Experimental hypersensitiveness to *Staphylococcus*, *Proc. Soc. Exper. Biol. and Med.*, 1935, xxxii, 945-948.
- THOMPSON, R., and KHORAZO, D.: Antigenic and biochemical properties of staphylococci, *Jr. Bact.*, 1937, xxxii, 51-52.
- HEGEMANN, G.: Untersuchungen über typen Differenzierung der Staphylokokken, *Centralbl. Bakt.*, I, O., 1937, cxl, 108-113.
- PERAGALLO, I.: Sulla possibile identificazione di eventuali tipi immunologici dello stafilococco, *Giorn. Batt. Immunol.*, 1937, xviii, 577-589.
- COWAN, S. T.: The classification of staphylococci by precipitation and biological reactions, *Jr. Path. and Bact.*, 1938, xli, 31-45.
- JULIANELLE, L. A.: Determination of staphylococcal types by fermentation of mannite, *Proc. Soc. Exper. Biol. and Med.*, 1937, xxxvi, 117-119.
- FLAUM, A.: Studies in staphylococci and staphylococcal immunity, *Acta Path. Microbiol. Scand.*, 1938, Suppl. 35.
- THYGESON, P.: Mannitol fermentation as an indicator of conjunctival pathogenicity of staphylococci, *Arch. Ophthalm.*, 1938, xx, 274-275.
- JULIANELLE, L. A., and HARTMANN, A. F.: The immunological specificity of staphylococci. IV. Cutaneous reactions to the type-specific carbohydrates, *Jr. Exper. Med.*, 1936, lxiv, 149-159.
- GOODNER, K., HORSFALL, F. L., JR., and DUBOS, R. J.: Type-specific antipneumococcic rabbit serum for therapeutic purposes. Production, processing, and standardization, *Jr. Immunol.*, 1937, xxxiii, 279-296.
- STOOKEY, P. F., and SCARPELLINO, L. A.: *Staphylococcus septicemia*, *South. Med. Jr.*, 1939, xxxii, 173-179.

BENIGN AND MALIGNANT GASTRIC ULCERS: THEIR RELATION AND CLINICAL DIFFERENTIATION *

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THE purpose of this paper is to consider briefly the relationship between benign and malignant gastric ulcers, the clinical differentiation of the two lesions, and the therapeutic implications.

RELATIONSHIP

A few years after Cruveilhier differentiated gastric ulcer from gastric carcinoma, Rokitsky described a case interpreted as showing the carcinomatous transformation of a benign ulcer. An enormous controversial literature has since developed regarding, first, the existence of carcinomatous degeneration in ulcer, and, secondly, the incidence of such a process. A critical review of the subject has led me to doubt the existence of such a transformation. The alleged evidence for such a change is based on pathologic and clinical findings. To support this viewpoint pathologically, carcinoma must be found and proof of the original benign nature of the lesion established. The difficulty in a given case does not consist usually in establishing the presence of the standard criteria of malignancy, but in proving the initial benign nature of the lesion. It is customary to demand that the floor of the ulcer be composed of dense, fibrous and granulation tissue not infiltrated with tumor cells and that there be complete destruction of an area of muscle corresponding in size roughly to the ulcer. Fusion or close approximation of the muscularis mucosae and muscularis at the edge of the ulcer and endarteritis obliterans are other signs suggestive of preëxistent benign ulcer. It is recognized, however, that none of these is pathognomonic of a preëxistent benign ulcer and that any and all of them may be found with primary carcinoma. Histologically, therefore, the evidence of an initial benign ulcer in a carcinomatous lesion is never conclusive.¹

The clinical proof usually adduced is also not conclusive. The presence of epigastric distress for many years, even if it is of the typical ulcer type, may have no relation to the carcinoma, for numerous cases of neoplasm have been described as arising in stomachs containing gastric or duodenal ulcer but entirely independent of these lesions. Even the case described by Scott and Mider² of carcinoma occurring at the site of an acutely perforated gastric ulcer surgically repaired two years previously may be looked upon, and I think should be looked upon, as a slowly growing primary carcinoma which had undergone peptic ulceration. The presence of free acid in the gastric

* Read at the New Orleans meeting of the American College of Physicians, March 30, 1939.

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content has been looked upon as "the crucial factor" in the diagnosis of preëxistent benign ulcer.³ On the contrary, however, the evidence offered in support of this concept may equally well be interpreted to support the opposite view, namely, that acid gastric juice may destroy the carcinoma so completely and attack the normal tissue to such an extent as to mimic benign ulcer completely.⁴

The following case is described in considerable detail as illustration of this point. It shows the extent to which an apparently primary gastric carcinoma may undergo peptic ulceration with healing, scar-tissue formation, and even epithelization, and thus simulate a benign ulcer.

The patient, a male 50 years of age, entered the Clinics November 19, 1938, on the service of Dr. A. Hughes Bryan complaining of sharp, knifelike pain in the middle of the sternum of 12 hours' duration. Occasional attacks of vomiting had occurred during the preceding year, approximately one every three to four weeks, coming on one to one and a half hours after meals. Five months prior to admission the patient became conscious of a heavy, dragging sensation in the epigastrium. A roentgen-ray examination was said to have disclosed the presence of a gastric ulcer for which a regimen of milk and cream and powders was prescribed. A subsequent roentgen-ray examination was said to have disclosed no ulcer. The patient continued the milk and cream and powder program, felt improved, but lost 20 pounds in three months. There was no history of indigestion or epigastric distress prior to June 1938.

Physical examination disclosed no significant abnormality. The red blood count on admission was 3.95 million; hemoglobin, 72 per cent (Dare); white blood count, 10,000. The histamine test of gastric secretion December 23, 1938, revealed a maximum free acidity of 106 with a maximum 10-minute volume of 24 c.c. The stool examinations for occult blood varied from negative to strongly positive. Roentgen-ray examination on November 21, 1938, had disclosed a frank early stage lesion of the seventh thoracic vertebra, presumably a metastatic neoplasm, and a lesion in the body of the sternum interpreted either as gumma or neoplasm. The gastric film contained a small, pointed projection at the lesser curvature of the stomach just proximal to the pyloric antrum, interpreted as being possibly a very small lesser curvature neoplasm with a tiny crater (figure 1). At a subsequent examination December 2, 1938, this small niche was not found. Two months later, February 3, 1939, the niche was again found roentgenologically and, in view of the gastroscopic findings, interpreted as an infiltrating, ulcerating type of carcinoma. Lesions noted in the right ischium, ilium, and femoral neck were interpreted as metastatic.

Gastroscopic examinations by Dr. Rudolf Schindler were reported as follows:

December 15, 1938. Definite pathology is found at the angulus. It is not a parabolic curve. Its anterior branch presents a protruding node. On the top of its arch, a large, rather round, dark red, mucosal hemorrhage is seen below which the arch is flattened and stiff. There are nodes protruding from the posterior wall of the antrum. The stiffness of the infiltrated portions is marked. No craterlike excavation or ulceration is observed. The mucosa is pale throughout but not atrophic. At several places pigment spots and stripes are observed.

Impression: Diffusely infiltrative lesion of the angulus. (I do not believe this is a simple gastritis; probably it is a type IV infiltrative carcinoma, although other infiltrative lesions cannot be excluded with certainty.)

December 22, 1938. The interpretation of this gastroscopic picture is exceedingly difficult. The lesions today are entirely different from those seen at the last examination. The angulus and the contracting pylorus are well observed. The angulus is not entirely round, but it is less stiff than it was when seen before. The dark red

hemorrhage has disappeared. Instead of it, a very small, round, yellowish, superficial ulceration is seen with many superficial mucosal hemorrhages in the vicinity. The entire mucosa is paler than at the last examination. I should estimate the hemoglobin content, from the aspect of this mucosa, to be not higher than 50 per cent.

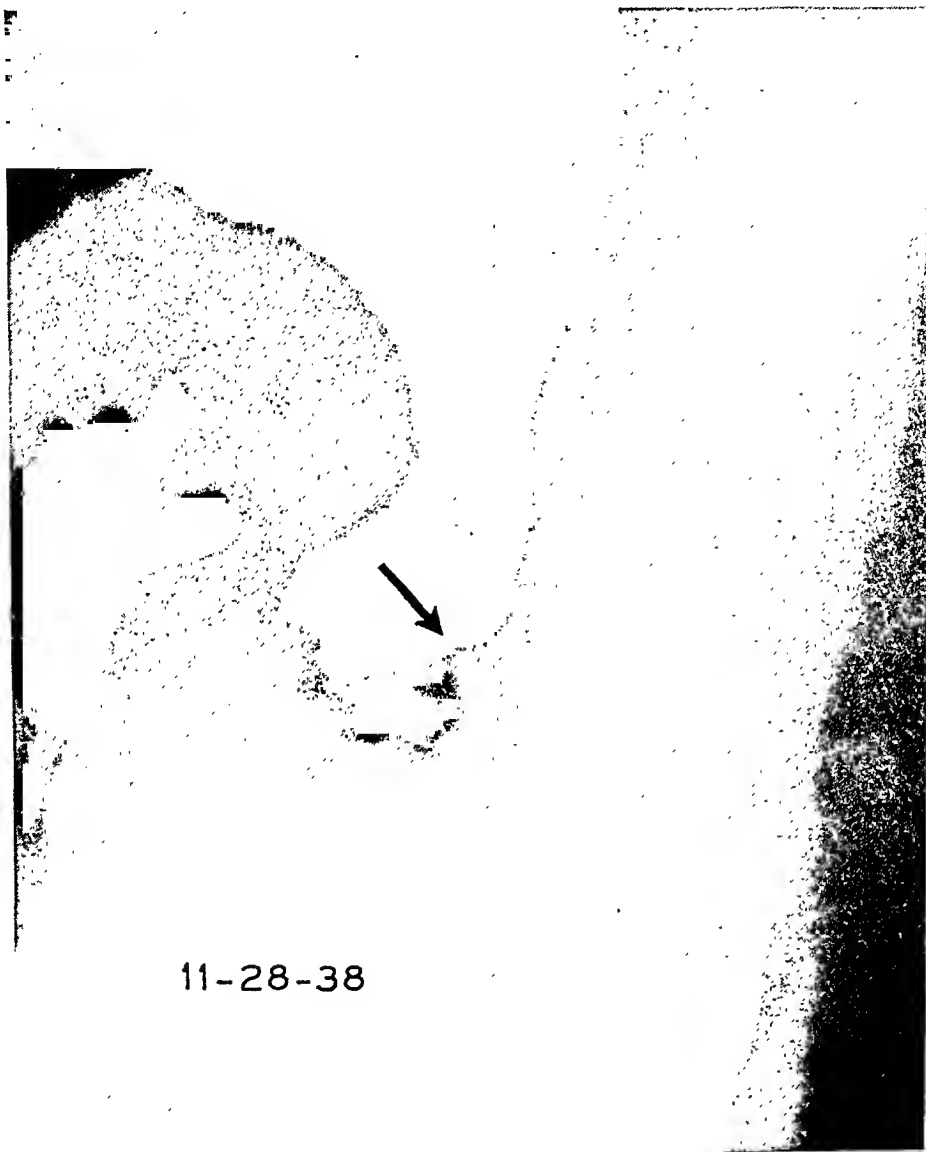


FIG. 1. Small, penetrating, carcinomatous ulcer of the lesser curvature.

Impression: There is definite pathology of the stomach present, but I am unable to make a definite diagnosis. The reduction of the infiltration speaks against malignancy. The small ulcer at the angulus probably is a gastritic erosion. Most conspicuous are the pallor and the many mucosal hemorrhages. I remember a similar case in which a diffused hemorrhagic condition covered a diffusely infiltrated carcinoma.

December 31, 1938. Again the picture has changed. The entire gastric mucosa looks extremely pale and I should think the hemoglobin cannot be over 20 per cent. . . .

At the highest point of the angulus, exactly in the lesser curvature, the interesting phenomenon of an acute mucosal bleeding is observed. A dark red bead of clotted blood is seen hanging into the lumen and lighter red blood falls down in drops from the tip of this clot into the stomach. This continuous bleeding makes this examination difficult; nevertheless, I have the impression that the anterior margin of the angulus is slightly infiltrated. . . .

Impression: (1) Acute, diffusely bleeding lesion of the angulus. I am unable to determine the exact nature of this lesion. (2) Extreme pallor of the gastric mucosa.

February 1, 1939. The examination is a complete one. The entire antrum is seen, even its lesser curvature. The pylorus contracts regularly and energetically. I have the indefinite impression that the upper portions of the anterior wall of the antrum are slightly stiff and protruded. In the lesser curvature above the angulus, again definite pathology is found. There is an infiltrated area approximately 4.5 to 5 cm. in diameter which showed many nodes and nodules. No sharp limit to this infiltration is seen. In its center a yellowish ulceration is observed, the margin of which is not sharp at all but blending throughout with the surrounding mucosa. The upper edge of the infiltrated area is seen 9.5 cm. below the cardia. No mucosal changes, especially no atrophy, are observed.

Impression: I cannot hesitate any longer to make the definite diagnosis of an ulcerative carcinoma, type IV, in the lesser curvature above the angulus.

The pain over the sternum continued, pain in the right hip and leg appeared, loss of weight and strength progressed. Pallor developed and increased. The red blood count dropped to 2.36 million with a hemoglobin of 49 per cent on December 31, 1938, to 1.93 million with a hemoglobin of 38 per cent on January 4, 1939, and, in spite of seven blood transfusions of approximately 600 c.c. each, reached a low of 800,000 on the day of death, February 5, 1939. The terminal picture was that of thrombocytopenic purpura and anemia secondary to extensive carcinomatosis.

At autopsy (Dr. Paul Steiner, Department of Pathology), the essential final anatomic diagnoses were:

1. Small, ulcerated, prepyloric adenocarcinoma of the stomach.
2. Independent carcinoma, or implantation metastasis in the mucosa of the gastric fundus.
3. Massive carcinoma metastases to the skeleton. Minute carcinoma metastases to lymph nodes, spleen, and lung.
4. Atrophic gastritis.
5. Marked anemia.
6. Fatty degeneration of the myocardium, liver, and kidneys.
7. Extramedullary hematopoiesis in the spleen and liver.

The gastric lesion appeared grossly as a benign ulcer 1 cm. in diameter and 1 to 3 mm. deep, located on the lesser curvature 4 cm. from the pyloric ring. Its margins were slightly reddened and slightly rolled although soft and pliable. The ulcer floor was clean except for mucus. External to this point, the serosa of the stomach showed a little puckering but no thickening. The gastric mucosa near the ulcer showed a number of soft, slightly elevated, edematous swellings. Grossly the ulcer showed a number of soft, slightly elevated, edematous swellings. Grossly the gastric ulcer and the adjoining linear scar had the appearance of peptic ulcer and not of ulcerated gastric carcinoma. Figure 2 is a section through the carcinomatous ulcer. The floor is composed of dense, fibrous tissue replacing all layers of the gastric wall. At the margins of the ulcer are scattered, imperfectly formed tumor glands and some diffuse growth of undifferentiated carcinoma cells. Figure 3 is a higher magnification of section 1 through the margin of the lesion showing normal mucosa on the right and carcinomatous infiltration on the left. Figure 4 from section 2 shows ulceration

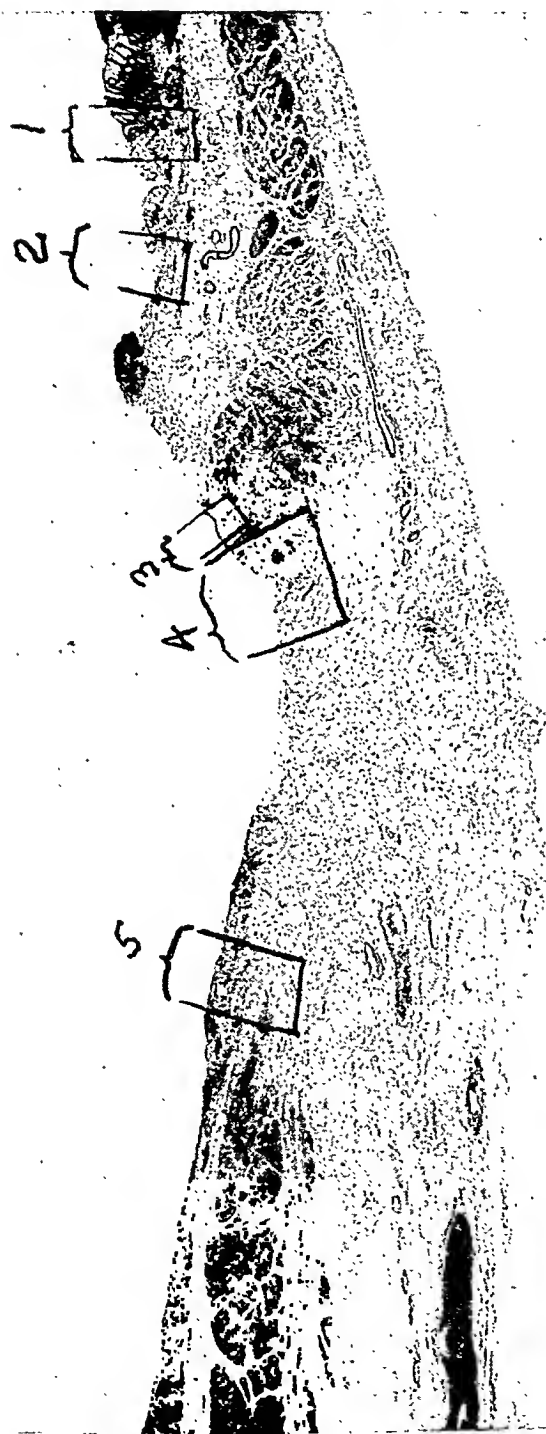


FIG. 2. Cross section through ulcerating carcinoma showing scar-tissue floor and general architecture of benign ulcer; X 6.

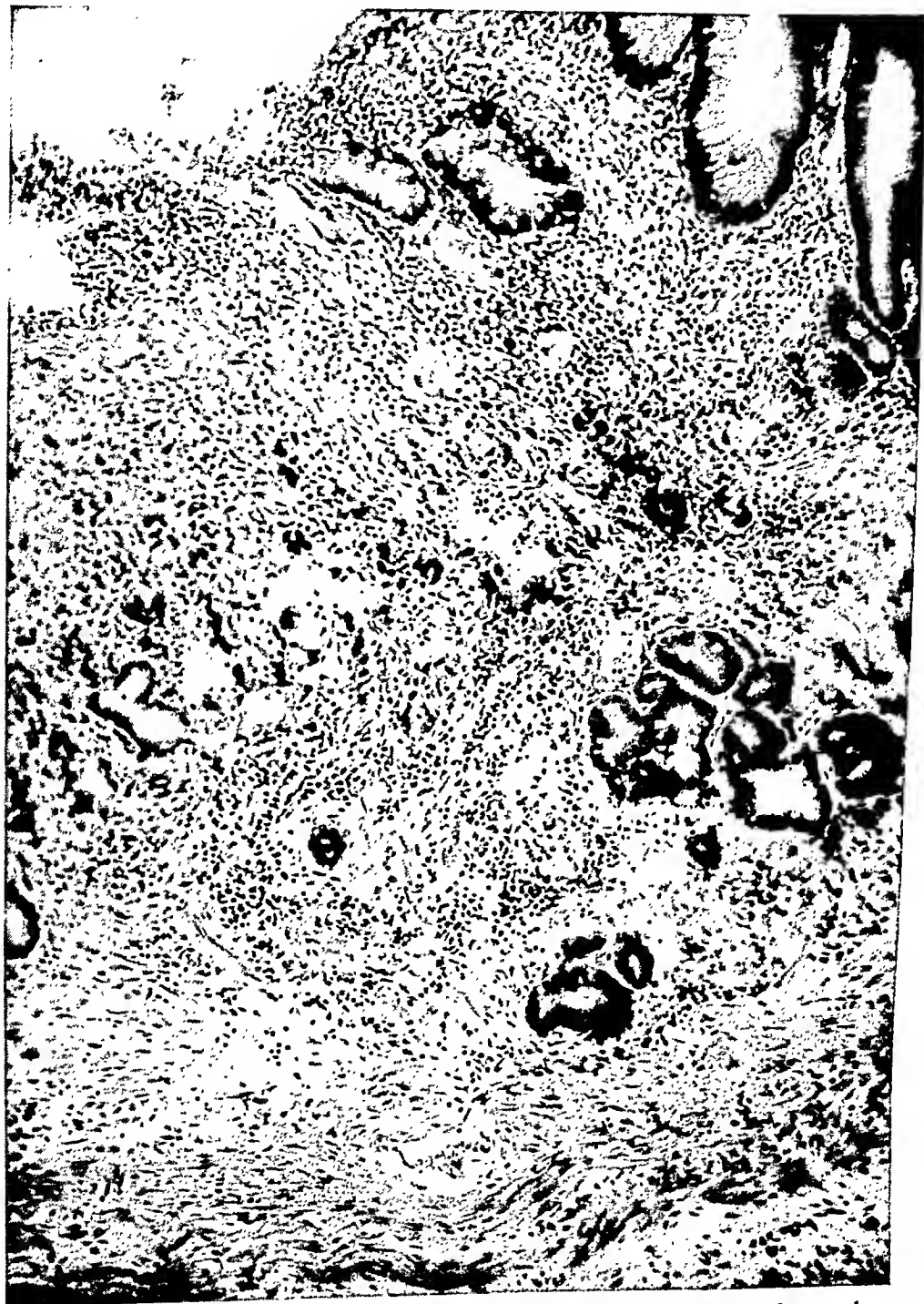


FIG. 3. Section through margin of ulcerating carcinoma showing edge of normal mucosa at right and carcinomatous infiltration at left; $\times 130$.



FIG. 4. Ulceration in carcinoma at edge of ulcer; $\times 130$.

in carcinoma, the muscularis mucosae being as yet intact. In figure 5 from section 3 the superficial layer of tumor cells is well shown. In figure 6 of section 4 this layer is seen growing down over, or only partially digested away from, the dense scar-tissue base. Figure 7 from section 5 in the left edge of the lesions shows diffuse adenocarcinomatous infiltration of the superficial layers of the mucosa and overlying noncancerous mucosa. The extensive carcinomatous infiltration is that of a primary gastric carcinoma, a conclusion quite in accord with the brief history, the extensive carcinomatosis, and the rapid clinical course. The structure of the ulcer must be ascribed to peptic ulceration of a primary carcinoma, producing thereby a lesion grossly indistinguishable from benign ulcer.

Extending laterally from the ulcer in the mucosa was a linear, slightly depressed and puckered scar up to 1 cm. wide and 4 cm. long, apparently lined with mucosa. Figure 8 is a cross section through this scar showing its complete reëpithelization. The carcinomatous infiltration of the epithelium with neoplastic glands beneath the muscularis mucosae is evident in figure 9.

In the fundus of the stomach about five inches from the ulcerated cancer, at a point where no lesion was grossly visible, an incidental microscopic section revealed a small superficial carcinoma located in the mucosa (figures 10 and 11). It was impossible to determine whether this was an implantation metastasis or a beginning independent cancer.

Elsewhere all portions of the stomach showed microscopic evidence of an atrophic gastritis of a moderate degree (figure 12). The mucosa was thin with a decrease in size of all parts of the glands, some cystic dilation of the glands, an increase in interglandular cells and interstitial stroma, large aggregates of lymphoid cells, and fibrous thickening of the submucosa. The changes of atrophy and metaplasia predominated over those of inflammation.

The skeleton was the site of a remarkable, diffuse, metastatic, adenocarcinomatosis involving all bones examined except a tarsal bone. Thus, dorsal and lumbar vertebral bodies, sternum, clavicle, ribs, and ischium showed replacement of the red marrow by tumor. The sternum was enlarged because of new bone produced on the surface of the old cortex by periosteal stimulation of tumor, but "while the density of the bones was about normal, the structure was not" (figure 13).

The case evidently falls in the group of diffusely infiltrative carcinomas thoroughly reviewed recently by Jarcho.⁵ Evidence of initial malignancy is to be found in the brief clinical course (eight months), the early appearance of widespread metastases, the small ulcer with tumor cells infiltrating both edges and covering a portion of the base with scattered foci in the base, the carcinoma in the mucosa lining the epithelized superficial scar adjacent to the ulcer, and the gastritic changes in the mucosa elsewhere. The small carcinoma accidentally found in a fold high in the stomach could perhaps be explained as an implantation metastasis, but a more probable explanation is that of primary multicentric carcinoma developing in a mucosa undergoing neoplasia. The presence and distribution of the malignant cells in the epithelium covering the scar, figures 8 and 9, may be interpreted as being in accord with this concept. The structure of the ulcer simulating, as it does, a benign lesion with healing (even the complete healing of one defect!) may be attributed to peptic digestion (histamine free acidity, 106!). The identical gross appearance of benign and malignant ulcer is not surprising when one bears in mind that the pathogenesis of the two lesions may be in part the same, namely, "acid attack" or "peptic digestion."⁶ Car-



FIG. 5. Edge of base of ulcerating carcinoma showing superficial layer of tumor cells; $\times 160$.



FIG. 6. Scar-tissue base of ulcer with layer of cancer cells on surface of upper right edge; $\times 60$.



FIG. 7. Left edge of ulcerating carcinoma. Diffuse infiltration of adenocarcinoma overlying noncancerous mucosa; $\times 115$.



FIG. 8. Section of scar adjacent to ulcer showing epithelization with mucosa containing nests of tumor cells; $\times 5$.



FIG. 9. Same section as in figure 8, showing carcinomatous infiltration of the epithelial layer with neoplastic glands beneath the muscularis mucosae; $\times 120$.



FIG. 10. Section of fold in fundus showing early carcinoma; $\times 30$.

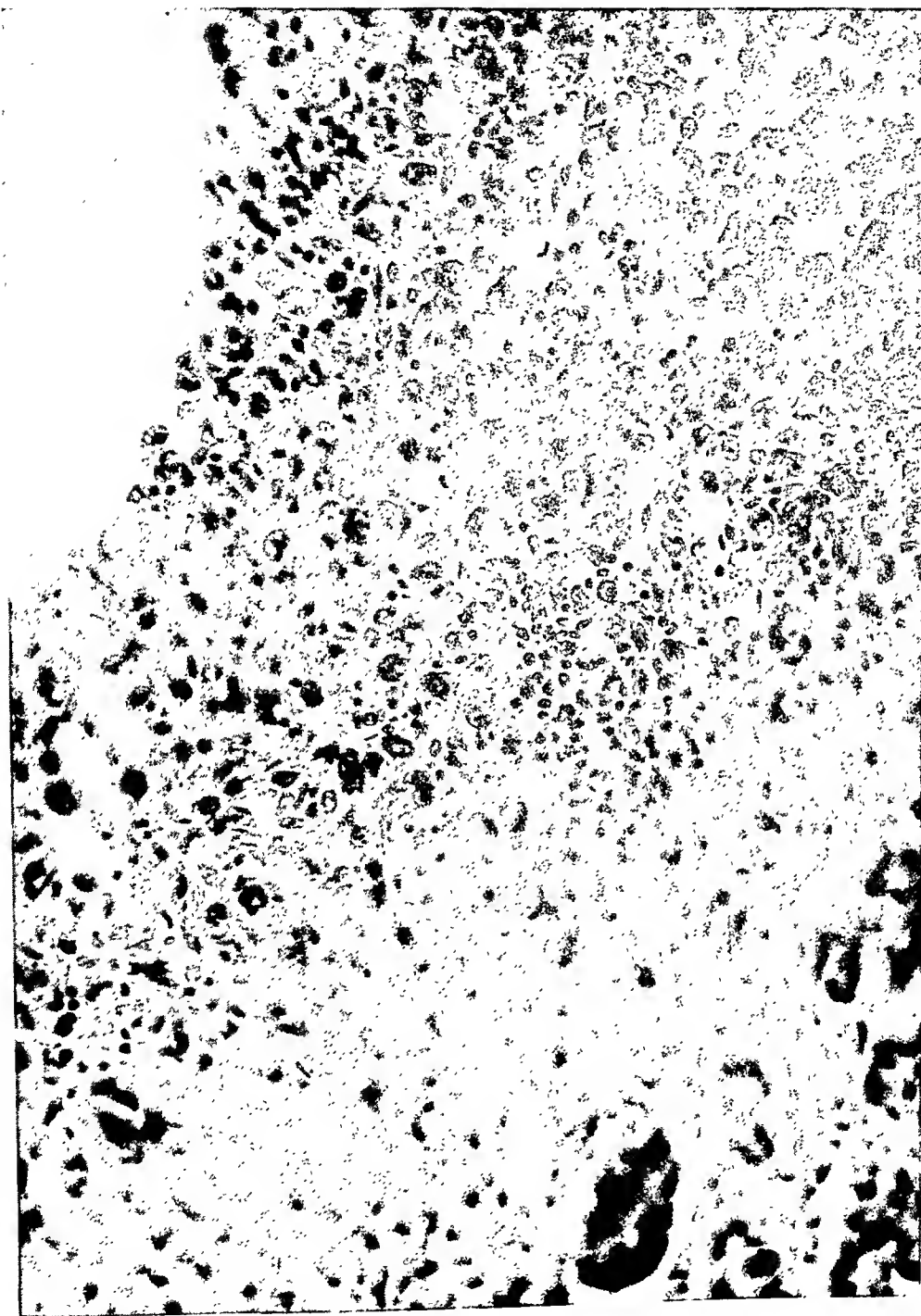


FIG. 11. Section of tumor in figure 9 showing numerous abnormal cells and abnormal, mitotic figures; $\times 300$.



FIG. 12. Atrophic gastritis with fibrous tissue thickening of submucosa in the pyloric region not far from the ulcer; $\times 130$.

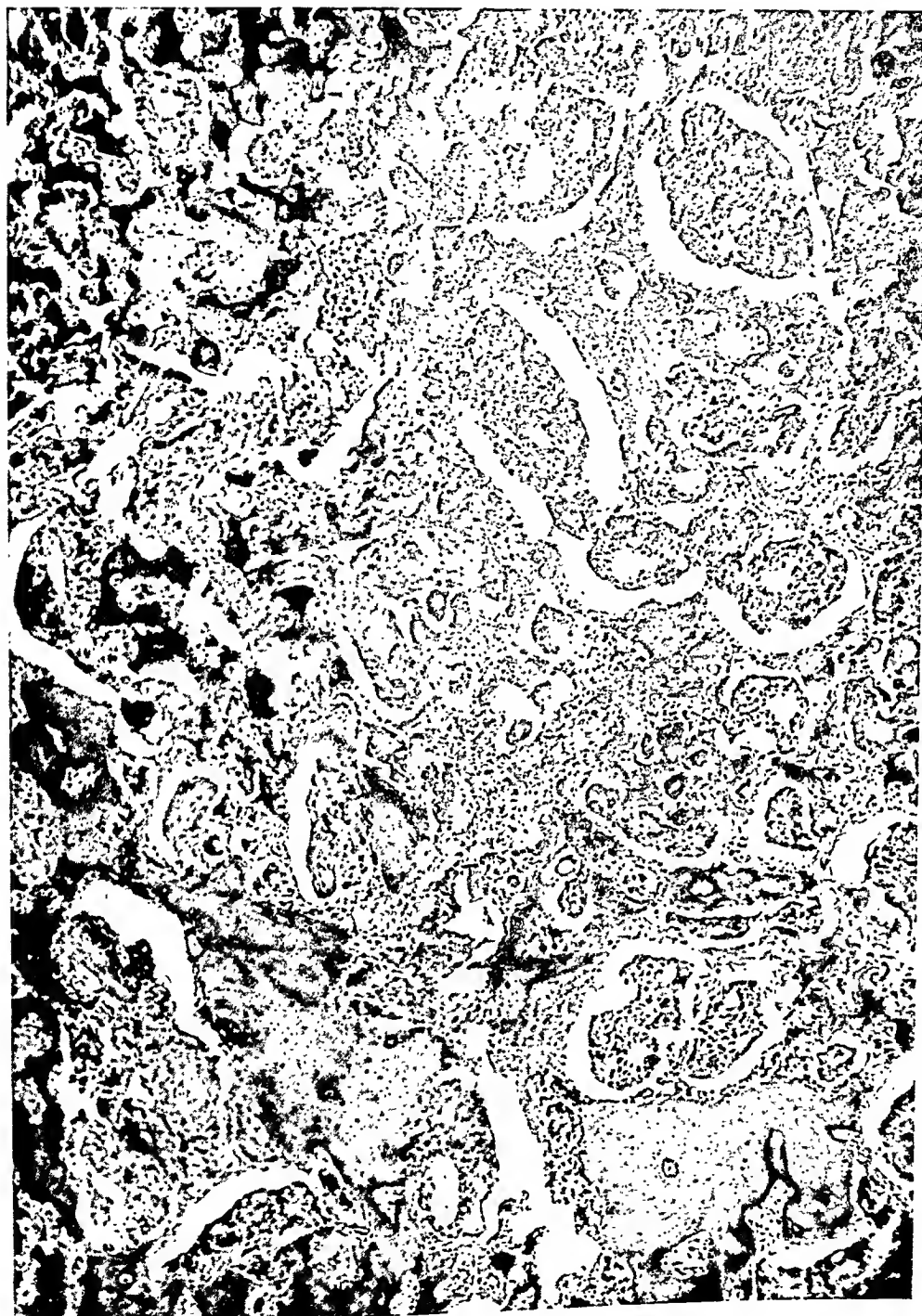


FIG. 13. Metastatic adenocarcinoma infiltrating the bone marrow (sternum); $\times 75$.

cinomatous mucosa is probably less resistant than normal tissue to the digestive action of acid gastric juice.

DIFFERENTIATION

If the concept of acid digestion of carcinomatous gastric tissue be accepted, and particularly if the concept of acid digestion of normal gastric tissue in both benign and malignant ulcer be accepted, the theoretical possibility of the complete inseparability of the two lesions must be conceded. In practice, the differentiation can, as a rule, be made, but the criteria must be critically examined. It is important to recognize at once that, while there is no pathognomonic sign to prove the benign nature of an ulcer, the total evidence available may be sufficient to make this diagnosis highly probable and, in the course of time, certain. Opinions differ as to whether in general, or indeed in a particular case, the evidence is sufficient to justify medical management and delay. Bloomfield⁷ has pointed out that if the incidence of error in the clinical differentiation is not greater than the mortality rate from subtotal gastrectomy, the delay necessary is justifiable. It is difficult to be positive on this point, for the accuracy of the clinical differentiation varies from person to person just as the mortality rate from resection varies from individual to individual. Both depend upon the skill of the physician or surgeon and upon the special conditions present in the case under consideration.

The important differential points and the difficulties involved are the following:

1. Age. This is not of great diagnostic value, for carcinoma occurs in the third decade and benign gastric ulcer is common in the later decades of life.

2. Duration. A long history is said to favor benign ulcer and a short one malignancy, but carcinoma may develop in a patient with chronic distress of other origin and, conversely, benign ulcer frequently gives a history of only a few months' duration.

3. Periodicity. If the *same* distress has recurred at intervals for several years, the probability of a benign lesion is greatly enhanced, but malignant lesions, if very slow growing, may display asymptomatic periods. Benign ulcer, on the other hand, may give no history of periodicity.

4. Relationship of the distress to meal taking, with relief after taking food or alkali, or following emesis is of no differential value, for it is frequently encountered in carcinoma as well as in benign ulcer.

5. A change in the nature of the distress is often considered important, but this occurs in both lesions.

6. Loss of appetite, loss of weight, loss of strength, coffee-ground emesis, melena, and anemia may occur in both conditions.

7. Gastric Analysis. Of paramount importance is the demonstration of free hydrochloric acid in the gastric secretion, for a diagnosis of chronic

benign ulcer is *not* acceptable in the presence of *continued proved* (histamine) *achlorhydria*. Carcinoma, on the other hand, may occur, as in the case described, in the presence of normal acid values (free hydrochloric acid with histamine to 106!). Large numbers of Opler-Boas bacilli and lactic acid in abnormal amounts are not seen in benign ulcer.

8. Stool Analysis. The continued absence of occult blood from the stool speaks strongly (but not positively!) for a benign ulcer whereas the continued presence of occult blood after two or three weeks of treatment speaks equally strongly for carcinoma.

9. Roentgenologic Manifestations. The various criteria in use for the roentgen-ray evaluation of a given ulcer crater are related chiefly to the location, size, and depth of the lesion and the mucosal pattern about it.

a. Ulcers of the greater curvature are almost always malignant. According to Eusterman and Balfour⁸ there are, in the files of the Mayo Clinic, records of only four benign ulcers of the greater curvature. Matthews⁹ reviewed the literature carefully in 1935 and found only 22 cases described in sufficient detail to warrant that diagnosis.

b. Ulcers of the prepyloric or antral region are likely to be malignant, but many of them are not. Pathologically, the antrum is the favorite site for the development of carcinoma. Konjetzny¹⁰ found 82 per cent of the gastric carcinomas to involve the antrum. Graham¹¹ found that 94 per cent of the ulcers situated between the incisura and the pyloric vein were histologically malignant. Holmes and Hampton¹² considered the majority of these prepyloric ulcers to be malignant.

c. Size is of relatively little practical value in the differentiation. Small lesions may be carcinomatous (see figure 1), and many large craters are benign.¹³

d. Benign ulcers usually give the appearance of extending beyond the normal confines of the gastric lumen whereas carcinomatous craters do not. Exceptions, however, are not infrequent.

e. Tumefaction, appearing as a halo about an ulcer crater, may often be seen by the use of manual pressure in both benign and malignant lesions, due in the former to edema and inflammatory swelling, in the latter, to these factors plus neoplastic infiltration.

f. The meniscus sign of Carman,¹⁴ consisting of an ulcer crater located beneath the level of the lesser curvature and demarcated by a zone of tumefaction appearing as a halo, almost invariably denotes carcinoma.

g. In benign ulcer the adjacent mucosal pattern is usually smooth except for folds radiating to the lesion. Such radiating folds may also be seen in carcinoma but they are usually less numerous. Parallel folds ending abruptly at the margin of the lesion are strongly suggestive of malignancy. In neoplasm the mucosal pattern about the crater may be coarsely nodular.

h. Benign craters are usually smooth or slightly irregular; malignant craters are often so, but *markedly irregular* or *ragged* craters are almost

always malignant, the irregularity being due to the nodules about the margins.

i. Under adequate therapy the benign ulcer crater diminishes rapidly in size.¹⁵ Complete disappearance of the roentgenologic crater, in the light of our present knowledge and assuming the use of satisfactory technic, speaks *very, very strongly* in favor of a benign lesion.

10. Gastroscopic Appearance. In experienced hands the gastroscope is of great differential value indeed, but it is not infallible. Attention is called to the fact that although, in the case cited in detail in the beginning of this article, Schindler, in his gastroscopic diagnosis, wavered as to the type of infiltration present, he did not think it necessary to consider the possibility of a benign lesion. To the pathologist, Dr. Steiner, however, the ulcer appeared grossly benign. The difference in the antemortem and postmortem appearance may be due, as Schindler and Steiner suggest, to an antemortem stiffness of the mucosa produced by the marked fibrosis throughout the submucosa. The benign ulcer, according to Schindler,¹⁶ is generally crater-like, rarely shallow; its floor is whitish yellow and not often brownish in color, although after an acute hemorrhage it may be dark red. Its edges are sharp, often partly undermined. The adjacent mucosa in early lesions is often normal; later there may be marked inflammation of the surrounding mucosa but rarely of the entire stomach. Converging folds occur. The carcinomatous ulcer, however, is characterized by less sharp edges so that the ulcer floor seems to blend with the mucosa. The floor is irregular and contains nodules, nodes, or ridges. It is occasionally whitish or yellowish in color but more frequently brown, brown-red, violet, gray or a dirty color. The malignant ulcer is usually elevated, appears to lie on a hill, and therein differs from the benign ulcer. The adjacent mucosa may be nodular. Schindler contends that it is easier to differentiate benign and malignant ulcer gastroscopically than in the gross appearance of the resected specimen because of the color nuances produced by the circulating blood and also perhaps because of the stiffening produced by the fibrous, submucosal infiltration.

It is clear that none of the criteria mentioned is pathognomonic of a benign lesion, unless it be the roentgenologically and gastroscopically *observed* and *proved*, *complete* healing of an ulcer. The epithelized scar adjacent to the ulcer, in the case described in detail in this article, might suggest that even proved healing does not completely disprove malignancy. Such a state of affairs, however, has yet to be demonstrated clinically. In spite of the lack of pathognomonic signs of benign ulcer, the accuracy of the clinical differentiation of the two lesions, if one weighs carefully all of the evidence, is, I believe, very high, but precise statistical figures cannot, as yet, be given. Individual factors of interpretation, of cases to be included or excluded, color all statistics on the subject.

The therapeutic implications of the foregoing considerations are debatable. The surgeon may find in them ample justification and indication for

advising immediate, subtotal gastrectomy in all cases of gastric ulcer. Bloomfield¹⁷ concluded that the errors in differentiation do not exceed the mortality rate of resection—a conclusion I share but cannot prove. A further consideration is the fact that end results of gastric resection for carcinoma, even the so-called “early carcinomas,” are not yet sufficiently impressive to warrant indiscriminate resection for benign ulcer. The practical plan of carefully following for a few weeks the lesions which appear to be benign is justifiable, and, I think, to be commended, provided the *course* of the lesion is actually studied. The particularly significant points to be observed are: (1) The disappearance and then the continued absence of occult blood from the stool, and (2) rapid diminution in the size of the crater as seen roentgenologically and gastroscopically. One can never rest content until the diagnosis of benign gastric ulcer is proved objectively by complete healing or by careful histologic examination. It is perhaps not necessary to add that patients with gross ulcers and histamine-achlorhydria, patients with ulcers of the greater curvature, and patients with questionable ulcers of the antrum should be promptly subjected to partial gastrectomy, for such lesions are usually malignant.

CONCLUSIONS

1. The existence of carcinomatous degeneration in benign ulcer remains to be proved conclusively.
2. Peptic ulceration of carcinoma may produce a lesion grossly indistinguishable from benign ulcer.
3. Although there is no pathognomonic sign to indicate the benign nature of a lesion, the total evidence available from careful study permits the clinical differentiation of benign and malignant gastric ulcer with a high degree of accuracy.

REFERENCES

1. KLEIN, S. H.: Origin of carcinoma in chronic gastric ulcer, *Arch. Surg.*, 1938, xxxvii, 155.
2. SCOTT, W. J. M., and MIDER, G. B.: Malignancy in the chronic gastric ulcer, *Am. Jr. Surg.*, 1938, xl, 47.
3. BLOOMFIELD, A. L.: The diagnosis of early cancerous changes in peptic ulcer, *Jr. Am. Med. Assoc.*, 1935, cix, 1197.
4. SCHMIDT, A., cited in MOSKOWICZ, L.: Über einen Fall von jungem “Ulcuscarcinom” des Magens, *Virchow's Arch. f. path. Anat.*, 1924, ccliii, 511.
- NIELSEN, N. A.: About the choice between medical and surgical treatment of ulcer ventriculi s. duodeni, *Acta chir. Scand.*, 1922–23, lv, 57.
- HAUSER, G.: Zur Frage von der krebsigen Entartung des chronischen Magengeschwürs, *München. med. Wchnschr.*, 1910, lvii, 1209.
- STROMEYER, F.: Die Pathogenese des Ulcus ventriculi, zugleich ein Beitrag zur Frage nach den Beziehungen zwischen Ulcus und Carcinom, *Beitr. z. path. Anat. u. z. allg. Path.*, 1912, liv, 1.
- ASCHOFF, L.: Über die mechanischen Momente in der Pathogenese des runden Magengeschwürs und über seine Beziehungen zum Krebs, *Deutsch. med. Wchnschr.*, xxxviii, 494.

- EWING, J.: Relation of gastric ulcer to cancer, *Ann. Surg.*, 1918, lxxvii, 715.
- WILENSKY, A. O., and THALHEIMER, W.: Etiological relationship of benign ulcer to carcinoma of the stomach, *Ann. Surg.*, 1918, lxxvii, 215.
- KONJETZNY, G. E.: Der jetzige Stand der Lehre von der Beziehung des Magenkarzinoms zum Magengeschwür, *Deutsch. med. Wchnschr.*, 1920, xlvii, 286.
- EWING, J.: Beginnings of gastric cancer, *Am. Jr. Surg.*, 1936, xxxi, 204.
5. JARCHO, S.: Diffusely infiltrative carcinoma, *Arch. Path.*, 1936, xxii, 674.
6. PALMER, W. L., and RENSHAW, J. F.: Carcinoma ex ulcere—a consideration of the problem with especial reference to the rôle of acid gastric secretion (to be published).
7. BLOOMFIELD.³
8. RIVERS, A. B., and DRY, T. J.: Differentiation of benign and malignant gastric ulcers, *Arch. Surg.*, 1935, xxx, 702.
9. MATTHEWS, W. B.: Peptic ulcer involving the greater curvature of the stomach, *Ann. Surg.*, 1935, ci, 844.
10. KONJETZNY, G. E.: *Der Magenkrebs*, Stuttgart, Ferdinand Enke, 1938, p. 158.
11. GRAHAM, R. R., in discussion on SCOTT, W. J. M.: The possibility of malignancy as it affects the treatment of chronic gastric ulcer, *Ann. Surg.*, 1935, cii, 586.
12. HOLMES, G. W., and HAMPTON, A. O.: The incidence of carcinoma in certain chronic ulcerating lesions of the stomach, *Jr. Am. Med. Assoc.*, 1932, xcix, 905.
13. PALMER, W. L., SCHINDLER, R., and TEMPLETON, F. E.: The development and healing of gastric ulcer, a clinical, gastroscopic and roentgenologic study, *Am. Jr. Digest. Dis.*, 1938, v, 501.
14. CARMAN, R. D.: New roentgen-ray sign of ulcerating gastric cancer, *Jr. Am. Med. Assoc.*, 1921, lxxvii, 990.
15. SCHINDLER, R.: *Gastroscopy, the endoscopic study of gastric pathology*, 1937, The University of Chicago Press, Chicago, p. 256, figure 84.
- PALMER, W. L., and FERRY, J. L.: Paper to be published.
- MASS, M., and STEIGMANN, F.: Carcinoma in clinically benign gastric ulcer, *Illinois Med. Jr.*, 1939, lxxv, 120.
16. SCHINDLER,¹⁵ p. 265.
17. BLOOMFIELD.³

THE POSTGRADUATE PORTION OF MEDICAL EDUCATION *

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THE annual session of the American College of Physicians is an appropriate place to discuss this subject of medical education. These Fellows of the College are themselves all students; their purpose in attending this meeting is to study medicine; the meeting represents an important variety of medical education.

When our President honored me with his invitation to discuss the graduate phase of medical education, he in effect asked me this question: "What do you think about this problem?" My answer, such as it is, represents my own conclusion and is not to be taken as implicating any faculty, committee, or group.

First, medical education is a long business. Because it is long and involved, I propose to begin by outlining its general course and development as medical education is practiced in America. If one could only give a description of the stages of medical education as concise and clear as Osler's description of the stages of typhoid fever, the cause of understanding would certainly be aided.

Of course the whole educational process bears on the training of doctors. Our discussion may begin, however, with the college training that precedes admission to medical school. If we were actually talking about typhoid, we could discuss here the incubation period and the prodromal symptoms. As it is, we must use the phrase "pre-medical training." The functions of this period are at least two: to advance the liberal education which is the preparation for life, and to supply a ground work for subsequent professional activity. There is no reason to think that this preparation should be the same for all; there are many reasons for encouraging diversity of preparation and for keeping required work at a minimum. As the President of Harvard University pointed out at the meeting of the Council on Medical Education of the American Medical Association last month, the college courses of the pre-medical period should be selected by the student because they are of value in his education and development, and not because he hopes they will make a good impression on admission committees. There is a great opportunity for improving the effectiveness and diminishing the confusion of this period by consultation between college faculties and medical school faculties, but in the main the responsibility for the quality and content of pre-medical work belongs to the college. College faculties are concerned with the preservation of liberal education as well as with the development of pre-professional education and it is a good principle of administration to see that primary responsibility is clearly placed.

* Read at the New Orleans meeting of the American College of Physicians, March 27, 1939.

The second period of medical education is the basic four-year course in the medical school. This may be compared to Osler's "fastigium"—the height of the disease, the period of continued fever. This period appears, at least to teachers in medical schools, to be the indispensable center of medical training. As specialization develops, this basic training becomes not less but more important. The basic medical course is the doorway through which men pass to all the fields of medicine. It still constitutes the most powerful influence tending to unite the varied fields of medical work and to prevent the isolation of specialists—an isolation that may result in a dangerous tendency to deal with parts of problems and parts of patients. This central or basic training is altering rapidly under the impact of the advance of medicine. It is becoming, on the whole, *less vocational* and more basic, and this change will probably go further. Even now medical schools do not, in general, prepare their students to practice medicine to the same degree that they did 20 years ago. They do pretty well, in my opinion, if they supply a foundation on which subsequent vocational training and experience may be firmly based.

This point of view is widely accepted. Thirteen schools in the United States and four in Canada make an internship a prerequisite for the M.D., and 20 state boards (plus Alaska and the District of Columbia) require such an internship as a condition of licensure. Such a hospital period of intensive vocational experience, under direction, but with increasing responsibility, is accepted as an indispensable portion of medical education. It may be expected that more state boards, as the bodies responsible for setting up the conditions of licensure, will so regard it. I take it as clear that the internship and its organization is the responsibility of the hospital. If it offers a high standard of work, a professional staff interested in the development of doctors, and reasonably good food, it will be a good internship and good men will apply for it. The internship is so important that it may be compared with the "crisis" in the course of typhoid fever, defining that term as "that period of change which may determine whether the result is to be good or bad."

That seems to end my typhoid metaphor. I refuse to consider the practice of medicine as convalescence from medical school or to get entangled in any light conversation about immunity to further education.

We come now, after considering a period of nine or 10 years of hard but intensely interesting work, to the problem of further training. Here we encounter the fields of graduate and postgraduate training, the chief theme of this discussion. No one has expressed more clearly the definition of these fields than Bruce, who writes, "By the term 'postgraduate' I refer to a program of teaching designed to maintain the practitioner at a suitable standard of professional fitness. By 'graduate' is meant those longer courses of study designed to prepare for teaching, research, or practice of a specialty."

For our purpose today, a few words about "training designed to maintain the practitioner at a suitable standard of professional fitness" will suffice, important as this field of work is. Assuming a good basic training, such *postgraduate work* is arranged to maintain the practitioner at a suitable standard, to keep him abreast of a rapidly moving current, and to aid him in continuing his growth, but not to change his spots by making him a specialist. The methods of postgraduate training are many. For example, one of the functions of education in general and of medical education in particular is to encourage the formation of the habit of scholarship. Such a habit may manifest itself through attendance at medical meetings (such as this one), through the utilization of personal experience as a means of education, through the taking of formal, so-called *refresher* courses, or through incessant and intelligent reading. Certainly the habit itself is more important than the means of putting it into action. But these means are certainly not unimportant and one of the interesting developments of recent decades in American medicine is the long series of thoughtful and earnest efforts to improve the opportunities for this sort of work. Happily the profession itself has decided that it wants opportunities for postgraduate training and is intelligently and with energy setting them up. Many medical societies have played an important rôle, aided by hospitals, schools, and health departments. Many plans take into account particular problems of particular regions or groups. In short, there are many opportunities for keeping up and they appear in general to be in good hands.

It is with the other aspect of post-intern training that my thoughts are now primarily concerned—what Bruce calls "graduate training" and defines as "those longer courses of study designed to prepare for teaching, research, or practice of a specialty." The preparation of men for special forms of practice is the main theme of these paragraphs, but in general the principles suggested will apply as well to the preparation of men for teaching and research.

A very brief perusal of the history of medicine will reveal the great importance of specialization. Special knowledge and special skill have been important factors in the progress of medicine and in the elevation of the standards of medical care. As part of the movement to improve the standards of practice, there have during some 20 years been set up a dozen or so special examining boards—such as the American Board of Internal Medicine—which are prepared to certify as to the qualification of individuals to practice various specialties. A large number of young men are now concerned with satisfying the requirements of these boards. These requirements then will have a determining influence on the type of opportunity that will be sought as graduate work. It is on the relation of these requirements and these boards to the general problem of medical education that I wish to offer one or two timid meditations.

Meditation number one is concerned with the subject of specialization

in general. It will, I daresay, be agreed that specialization is essential to modern practice and to the advance of medicine. Nevertheless, like all potent drugs, it can produce symptoms of intoxication if used in too great an amount or too high a concentration. Not only may special groups become concerned with parts of people and lose touch with the wider problem of the whole patient, but such groups may actually become isolated and lose some essential contact with other fields. This may not be very serious for the first generation of specialists in a given field, but it might be really grave for their students or their students' students. This suggests to me the daring hypothesis that perhaps no group should be wholly responsible for the training of its own successors. Is it not one of the advantages of bi-sexual reproduction that sons do not in all respects resemble their fathers?

Let me cite an example of the undesirability of special groups training their own successors. The last 30 years (which is the time equivalent to a human generation and about the interval between influenza pandemics) has seen a great and on the whole useful development of laboratories of so-called clinical investigation. These, in the main, have been organized by men deeply concerned with the problems of disease in patients and bringing to attack those problems the methods of anatomy, physiology, chemistry, physics, pharmacology, pathology, bacteriology, and genetics. For all their expertness in the exploration of disease these men are not (there are rare exceptions) professionals in the fundamental medical sciences as well; therefore they want to see coming into their laboratories a stream of young men trained in the basic sciences of today and not of the time when you and I were young.

On the basis of such general ideas, I venture with great trepidation and all due respect (and very seriously) to suggest that all special boards should include representatives of the general fields of medicine and surgery and that boards of broader interests (such as the American Board of Internal Medicine) should include representatives from at least some of the important specialties. It has even occurred to me to wonder whether the training of internists would not benefit from the proximity and counsel of surgeons. And vice versa.

Such a wise and generous action would have another useful function. There are examples in the history of medicine which indicate that special fields may be more important as special fields at one time than at another, or that they may exist at one period in a different relation to the general field of medicine or to other special fields than at another time. New specialties will arise, some present ones will change their form, or be absorbed back into the central body of Medicine. Rigidity of classification is biologically undesirable. This simple scheme might help to avoid it.

My second meditation has to do with the type of educational opportunity which should be available to those who seek development as experts in special fields. In this connection I quote the first paragraph of Dr. Pechey's preface to his English translation of "The whole works of that excellent

practical physician, Dr. Thomas Sydenham"; it was written in 1695:

"He that designs to attain to the right understanding of any Art or profession, usually chooses some Eminent Man of the Art to be his Guide and Pattern, by whose Directions and Example, joyned with a tolerable Capacity, and sufficient Diligence, he is and is deemed, at a stated Period, legally qualified for the Exercise of that Art he professes. And this I take to be the best and readiest way of attaining to the knowledge of any Art."

And I should agree with Dr. Pechey that so far as my experience with education goes, there is no substitute for working with competent leaders; the indispensable factors in this graduate phase of medical education are good men working in good hospitals. Dr. Halsted is quoted as having said once that the only important principle of making a medical school curriculum was to take the teaching away from the poor teachers and give it to the good ones.

Moreover it is a cause for rejoicing that many of the boards have recognized the importance of diversity of opportunity for men preparing for work in the same field. These boards wisely consider that they are primarily concerned with results, and the more originality and diversity the young men display in their approach to the special field, the better. There is another advantage to having the plan of training quite fluid; actually such elasticity is a protection to the ultimate standing of a given board. If a specific course of training is laid down it will certainly not be the best course for all men to follow. Not all independence and courage are dead, so that some men will follow their own ideas of training. Occasionally these may be very good, especially in rapidly changing types of practice. Under these circumstances we may be forced to recognize that some of the most effective people in a special field are not "properly" trained. In other words, success at state board examinations is not the ultimate test of medical education.

There are many other reasons for elasticity, freedom, and the avoidance of formal courses. One is that medical education has been entangled in overmuch conversation for many years. Students are just now escaping from the passive rôle of hearing many lectures into the more effective types of educational procedure in which they are active as well as the teacher. One of the dangers of a too formal development of graduate training is that there will be too much talking. This would be a backward, not a forward, step. Happily, the wisdom of medical men is such that most of the boards *are* concerned with competence, rather than with details of acquiring it.

Moreover, this general notion is in harmony with the astonishing breakdown of interdepartmental barriers that is now going on in teaching and research institutions. Investigation, instruction, and the care of patients are more often coöperative enterprises than they were. Even the archi-

ture of newly built schools and hospitals reflects this significant change in point of view.

My third meditation (and the final one) is concerned with the responsibility for opportunity for graduate work in the various special fields. Whose business is it? Here, I think, the water is perhaps deeper, certainly it is harder to see the bottom. Some aspects of it may, however, be made out. The men who compose the specialty groups have a large part to play. These internists, surgeons, pediatricians, obstetricians, and others will assume, as members of the staffs of hospitals where such training is carried on, the chief responsibility for establishing the standards and turning the machinery of graduate medical training. They are the people who will actually carry on the teaching.

Equally clearly, the hospitals where such training is offered are deeply concerned with the plans for graduate teaching. These plans are bound to have an influence on the organization of services, the growth of the resident system, and the educational responsibility of the hospitals.

It doesn't seem to me important that training for specialties should be in connection with medical schools and university hospitals, although of course it often will be. We are considering a very high type of vocational training, and such training, in my opinion, is not the first responsibility of the university medical school. The main concern of the medical school should continue to be the provision of the basic four-year course on which the splendid superstructures of graduate training are to be founded. These schools should not be placed in a position where the demands of graduate training could lower the standard of the undergraduate opportunity, any more than so-called premedical work should be allowed to injure a student's general education in college. And finally the many branches of organized medicine, including the American Medical Association and its special sections, and many special societies, have a deep interest in and responsibility for graduate education. For example, the American Board of Internal Medicine is the joint concern of the Section on Medicine of the American Medical Association and of the American College of Physicians. The American College of Surgeons, as another example, has already assumed an important phase of the responsibility for the training of surgeons.

Indeed the responsibility for graduate training is perhaps in some danger because it is shared by so many groups. Hospitals and their staffs, medical organizations, the state, and the medical schools, are all concerned. Joint understanding and effort of these diverse groups are absolutely indispensable conditions of any success at all in such an enormously difficult undertaking as graduate medical education. There is a great opportunity for leadership in the pursuit of this understanding by such an organization as the American College of Physicians.

CASE REPORTS

TRANSIENT FUNCTIONAL A-V HEART BLOCK INDUCED BY THE SWALLOWING OF FOOD; CASE REPORT*

By CHARLES SHOOKHOFF, M.D., F.A.C.P., and LOUIS BLUMENFELD, M.D.,
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THIS case of functional heart block is being reported because we believe this syndrome, and especially milder manifestations of it, may not be as uncommon as the few cases reported would lead one to believe. Instances of Adams-Stokes syndrome, due to overstimulation of the vagus and without apparent cardiac pathology, have been reported as early as 1875 by Thanhoffer¹ and in 1898 by Neuburger and Edinger,² and others. It was not until 1934, when Weiss and Ferris³ reported their thoroughly studied cases of syncope of reflex vagal origin—which they aptly termed “Vago-Vagal Syndrome”—that the present generation of physicians was reminded of the possibilities of functional A-V heart block, partial or complete, and its clinical manifestations.

Our case is almost a prototype of the one reported by Iglauer and Schwartz,⁴ and very similar to case 3 reported by Weiss and Ferris.³ These cases differ from the other instances of vago-vagal syndrome in that there is not only an absence of signs and symptoms of organic cardiovascular disease, but also an absence of signs and symptoms of organic disease in that organ (in this case the esophagus) from which the afferent impulses arise to reflexly, through efferent routes, influence the function of the A-V bundle. Dilatation of the esophagus, used by Iglauer and Schwartz, seems in this case as well to have a beneficial effect.

CASE REPORT

A. G., female, aged 58 years.

F. H.: Mother, aged 71 years, died of tuberculosis; father, 65 years, died of a cerebral hemorrhage; one brother, 49, died of cancer; four brothers are well.

P. H.: Measles in childhood. Sciatica at 25 years. Hemorrhoidectomy and removal of uterine fibroid in 1909. Menstruation at the age of 15 years; regular; no dysmenorrhea. Menopause at 45 years. Marital: married at 32 years; six pregnancies; first three pregnancies miscarried before three months; fourth, fifth and sixth pregnancies normal deliveries.

P. I.: In 1928 patient began complaining of a feeling of abdominal distention, gaseous eructations, and other vague symptoms; a diagnosis of a spastic colon was made. Soon after she noted difficulty in swallowing; she said “the food goes down to a certain point, it fills me up and I have to drink water to force the food down.” Patient also became dizzy when eating. A Sippy régime was instituted and she felt moderately well except for occasional attacks of dizziness when eating solid foods. In 1934 the attacks of vertigo became more frequent; and in addition loss of con-

* Received for publication June 21, 1938.

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FIG. 1. Showing Cardiospasm.

sciousness for a few moments on swallowing would occur. Following this the patient would become frightened and excited, and her face, neck and upper chest would become flushed. These attacks now occurred after almost every meal and continued up to 1936 when patient came to our attention. She was admitted to the hospital for

esophagoscopy. Her chief complaints were difficulty in swallowing food, choking sensation, attacks of dizziness and faintness, and not infrequently loss of consciousness. This syndrome occurred only on the swallowing of food; between meals the patient felt well and was able to carry on without gastrointestinal, cerebral or cardiovascular symptoms. The bowels were regular; she slept well; there were no nocturnal attacks; and her weight varied with the severity of the symptoms.

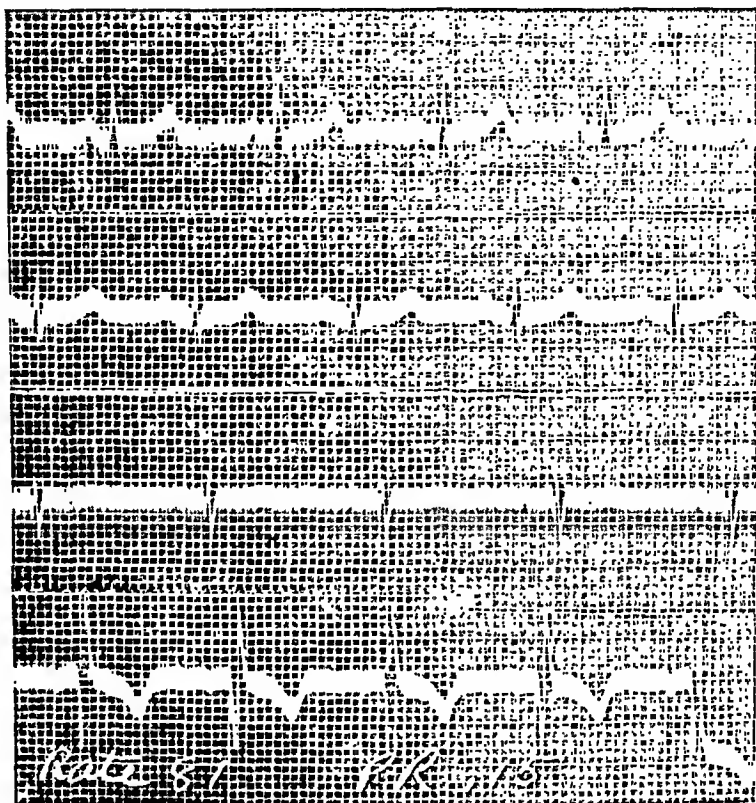


FIG. 2. Before eating.

P. E.: Weight 122 lbs. Height 62½ ins. B. P. 140 systolic and 88 diastolic. Pupils react to light. Eye grounds negative. Small, scarred tonsils; small angular glands. No other lymphatic glandular abnormalities. No palpable thyroid abnormalities. Radial, brachial and temporal vessels soft; dorsalis pedis and posterior tibial vessels normal. Heart normal in size and shape; regular sinus rhythm; sounds of good quality; no adventitious sounds; second aortic sound slightly accentuated; ventricular rate between meals approximately 82. Carotid sinus pressure reaction negative, both sides. Lungs, abdomen and extremities negative. Reaction to exercise normal.

Fluoroscopy: The heart and its individual chambers appeared normal in size and shape in all fluoroscopic positions, and no abnormal positional relationship to its surrounding structures was noted. Pulsations normal. The aortic knob was commensurate with patient's age. Lungs and diaphragmatic movements were normal. The barium-filled esophagus was slightly displaced in its upper part by the aortic knob; it was dilated and the cardiac end was completely constricted to a spindle-shaped end (figure 1).

Electrocardiogram: Before eating (figure 2)—showed a regular sinus rhythm, ventricular rate 82. There are no T-wave or R-T interval disturbances; slight left

axis deviation; the P-R interval in the second lead is 0.14 of a second; and the chest lead (Wolferth application) showed no abnormalities.

Patient was then given a dry sandwich (meat and bread), and continuous electrocardiographic curves were taken in the first lead. All symptoms were noted and correlated in time on these records. Studies of these electrocardiograms show that while chewing food (figure 3A) her heart rate went to 100; no P-R interval changes were noted. After swallowing several times, patient complained that her food was sticking and at the same time developed a brassy cough (figure 3B). The heart rate

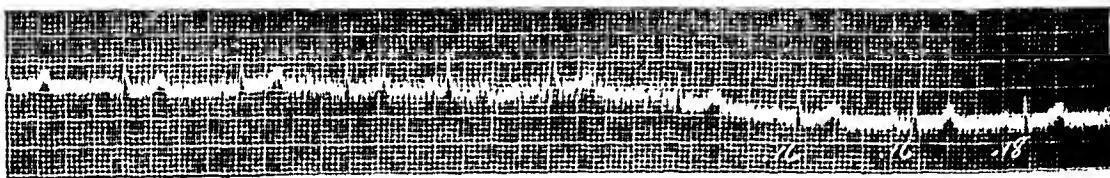
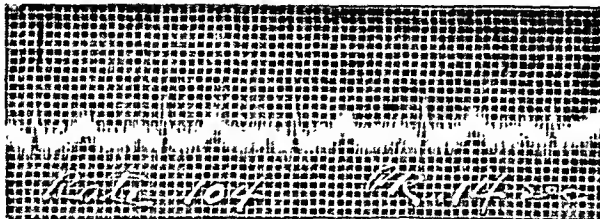


FIG. 3A (top). Chewing food before swallowing. FIG. 3B (below). Swallowing food; patient developed a brassy cough at this time. Ventricular rate now varied between 85 and 67; P-R intervals prolonged to 0.18 of a second.

dropped to 72; the P-R interval continued normal. The rate then became progressively slower and the A-V conduction time became 0.22 of a second, lengthened to 0.40 of a second, and then we noted a series of dropped beats; partial A-V 3:1 and 2:1 block. Patient complained of dizziness. She stopped eating; the rate slowly returned to 100 and the P-R interval to normal. This test was repeated several times with the same results (figure 4).

(The patient had not received belladonna or atropine for about two weeks before this examination. At no time during this examination did the patient become unconscious. She did become dizzy, faint and pale at times during these trials.)

Esophagoscopy: (Dr. Blumenfeld.) Cocaine 10 per cent solution; medium-sized Hesslinger esophagoscope. A constriction at the cricopharyngeus region of the esophagus was overcome by slight pressure. Another spastic obstruction was encountered at the region of the arch of the aorta. Below, the esophagus was ballooned out. The cardia was also found to be tetanic. The mucous membrane throughout was normal in appearance. No masses or other abnormalities were noted.

Impression: Esophageal spasm. The examination caused no symptoms.

Laboratory Data: Urinalysis—specific gravity 1.018; slight trace of albumin; otherwise negative.

Blood—4,700,000 red blood cells; 75 per cent hemoglobin; 4,900 white blood cells; 60 per cent neutrophils; 32 per cent small lymphocytes; 4 per cent large lymphocytes; 4 per cent eosinophiles.

Wassermann reaction negative.

Treatment and Interim History: It had already been noted that patient's symptoms were relieved by the administration of grain 1/100 atropine sulphate, t.i.d. For about two weeks before our studies, all medication had been discontinued and patient began again to experience the symptoms as described.

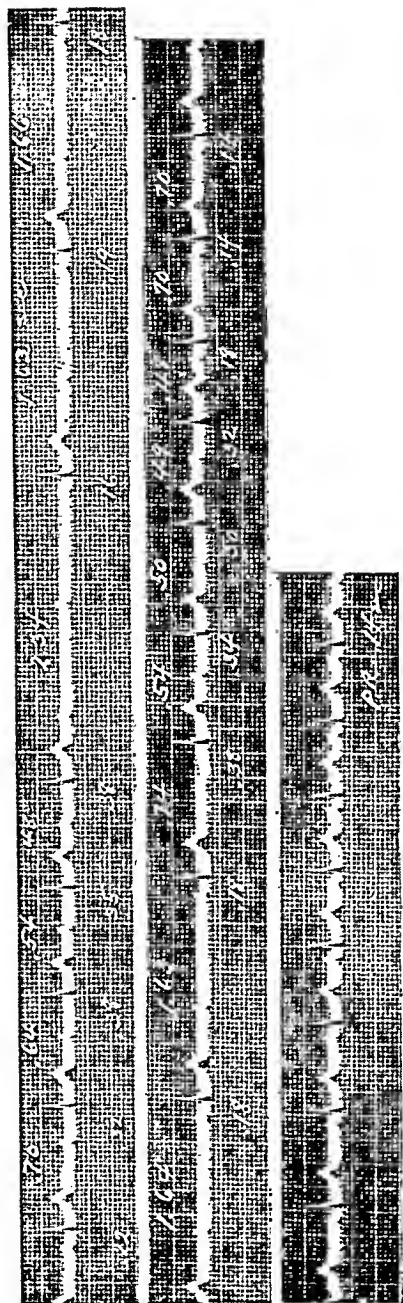


FIG. 4. Lead I—Continuation of figure 3. The numbers above the isoelectric line are the rest and recovery periods of the bundle; those below—P-R interval. The end of the second strip and the last strip, taken when patient had stopped eating.

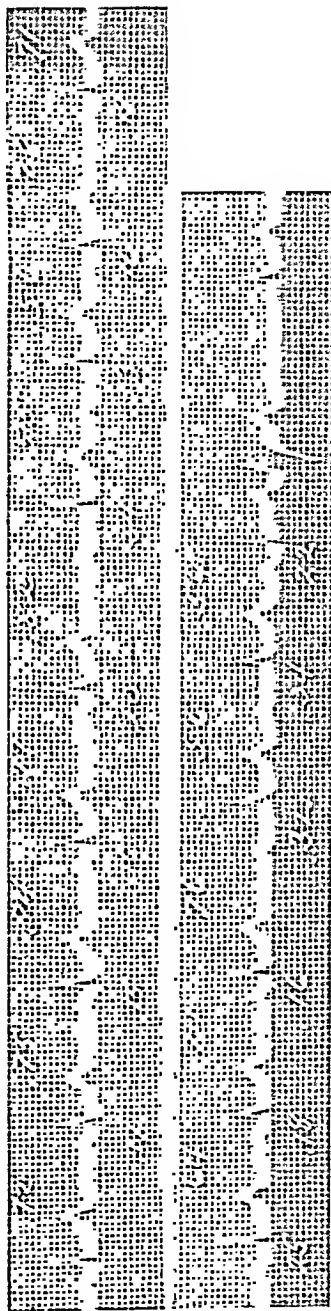


FIG. 5. Taken March 31, 1938—First Lead. Numbers above base line measure rest and recovery time of the bundle; numbers below, length of the P-R interval. Notice disproportion between length of rest and recovery time and the length of the P-R interval immediately following; notice also the sinus arrhythmia.

Subsequently the patient was given tincture of belladonna, minims 10, t.i.d., and esophageal dilatations, using a Hurst mercury filled esophageal dilator, 30 English, twice a week, were instituted. During the first week she had to coax her food along with sips of water; and while during the following two weeks she still encountered some difficulty in swallowing solid food, she experienced no difficulty with liquid and semi-solid foods. After the fourth week she had no more dizziness or syncopal attacks. The belladonna was then gradually reduced and finally discontinued; the esophageal dilatations were continued, but less frequently; no symptoms were produced by this procedure. Up to the present time patient has been comfortable and free from any sort of distress—without the administration of the atropine. During moments of excitement she may experience some difficulty in swallowing, but she has had no syncopal attacks for over a year.

On March 31, 1938, we repeated the examinations of 1936. Upon eating a sandwich patient experienced no symptoms and the electrocardiographic studies showed no change in rate or conduction time. When later she tried to swallow a thick bismuth meal, she complained "it could not go down." Upon fluoroscopying her we noted a cardiospasm of a lesser degree than had previously been observed. An electrocardiogram was taken while she was swallowing water to relieve her of the effects of the bismuth meal. This electrocardiogram, figure 5, showed a slowing of the cardiac rate, changes in conduction time, ventricular extrasystoles and subsequently a return to previous status.

DISCUSSION

We feel that this is a case of transient functional A-V heart block because at no time did patient show any subjective or objective signs of organic cardiovascular disease. In heart block due wholly or partially to pathologic changes in the bundle, there seems to exist—in the partial A-V block with drop beats of the Wenckebach type—a definite relationship between the rest and recovery time of the bundle (measured from the beginning of the ventriculogram, "Q" or "R" wave, to the upstroke of the next conducted P-wave) and the immediately following A-V conduction interval; the shorter the rest and recovery time, the longer the conduction time and vice versa. In these curves, however, this relationship does not always exist. In figures 4 and 5 one can see many instances—after rest and recovery time of 0.82 of a second, conduction of 0.34 of a second; after a rest and recovery time of 0.56 of a second, conduction time of 0.16 of a second; after rest and recovery time of 0.74 of a second, 0.16 of a second; after 0.77 of a second, 0.20 of a second. This change in relationship seems to show that the functional capabilities of the bundle are constantly varying with changes in vagal tonus, regardless of rest and recovery time. Changes in rate do not always occur at the same time as changes in conduction—there may be a considerable slowing of the sinus rate with no P-R interval changes, and P-R interval changes can occur without a slowing of the sinus rate; i.e., the increased vagal tonus may manifest itself both in the slowing of the sinus activity—predominantly through the right vagus—and lengthening of the conduction time—predominantly through the left vagus—at different times and in different degrees. This, of course, speaks for a functional causation of these phenomena.

It was noticed that upon swallowing the patient developed a brassy cough, lasting for a short time, similar to that which one hears in recurrent laryngeal involvement. This shows, we believe, that other efferent pathways may be involved in this vago-vagal syndrome.

At no time during a two year period have we obtained evidences of organic disease in the esophagus or in any of the surrounding organs.

SUMMARY

A case of transient functional A-V block, induced by swallowing of food has been presented. There are no evidences of organic disease. Dilatation of the esophagus seems to have a beneficial therapeutic effect in this type of case.

BIBLIOGRAPHY

1. THANHOFFER: Centralbl. f. d. med. Wissensch., 1875, p. 405.
2. NEUBURGER, TH., and EDINGER, L.: Einseitiger fast totaler Mangel des Cerebellums, Varix oblongatae, Herztod durch Accessoriusreizung, Berl. klin. Wchnschr., 1898, xxxv, 69.
3. WEISS, S., and FERRIS, E. B.: Adams-Stokes syndrome with transient complete heart block of vagovagal reflex origin; mechanism and treatment, Arch. Int. Med., 1934, liv, 931.
4. IGLAUER, S., and SCHWARTZ, B. A.: Heart block periodically induced by the swallowing of food in a patient with cardiospasm, Ann. Otol., Rhinol., and Laryngol., 1936, xlv, 875.

RENAL INSUFFICIENCY WITH TETANY IN AN ADULT; REPORT OF A CASE*

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CASE REPORT

THE patient was a Jewish woman, 48 years of age. Her symptoms appeared in 1905 when she was 29 and in her second pregnancy. At that time, she had the first of a long series of attacks which were characterized primarily by weakness of the muscles of the extremities of such severity that she was unable to walk or to raise her hands or arms. These attacks, varying in severity but essentially similar in character, continued to occur in this form at irregular intervals of one to six months until six months before she came under our observation in 1937, at which time their character changed as will be described. She was relatively symptom-free between episodes. The attacks were seasonal in that they were much more likely to occur in the winter or spring months and were much less frequent in the summer or during visits in the South. A typical attack might run a course of three or four days, relief apparently being obtained by large doses of a mixture containing potassium citrate and sodium salicylate. The level of serum calcium in 1926 was 13.0 mg. (?) per 100 c.c., and of blood urea 45 mg. per 100 c.c. Physical examination revealed no findings of significance and no definite diagnosis was made.

For four years after her marriage at 22 years of age, she had failed to menstruate. During that time, her weight fell to 97 pounds. She also gave a history of some polyuria and nocturia over a period of years. In the light of our present knowledge, it appears that these symptoms may have been of renal origin. Physical examination in 1934 again revealed essentially normal findings. The blood pressure was 110 systolic, 70 diastolic. At no time during her illness was the blood pressure elevated and at no time did she have any edema. The erythrocyte count was 4,890,000

* Received for publication June 2, 1938.

with 94 per cent hemoglobin; the white count was 11,150 with 52 per cent neutrophils, 1 per cent eosinophiles, 44 per cent lymphocytes, and 3 per cent monocytes. The urine showed a trace of albumin and many white cells. The level of the serum calcium was 8.24, the phosphorus 3.4, and the blood urea 39 mg. per 100 c.c. The basal metabolic rate was minus 8 per cent. Roentgen examination of the skull revealed no abnormalities. Examination of the eyegrounds showed a haziness of both optic discs, and mapping of the visual fields revealed a questionable defect in the left superior quadrant, but no change of diagnostic significance. Calcium lactate and large quantities of milk were prescribed and she was advised to take sunbaths. The flaccidity of the muscles during attacks at that time had spread to involve those of the neck as well as the extremities.

During the next several years, the levels of the serum calcium and phosphorus estimated at various intervals were sometimes normal but usually the calcium level was depressed and the phosphorus elevated. She continued to have attacks at somewhat less frequent intervals. Both the patient and her husband emphasized the fact that these attacks were those of muscular flaccidity, an observation borne out by the report of a physician who examined her at home during an attack in 1935. He reported muscular flaccidity, affecting particularly the neck and extremities and negative Chvostek's and Trousseau's signs. At that time, 15 c.c. of a 10 per cent solution of calcium gluconate intravenously did not relieve her.

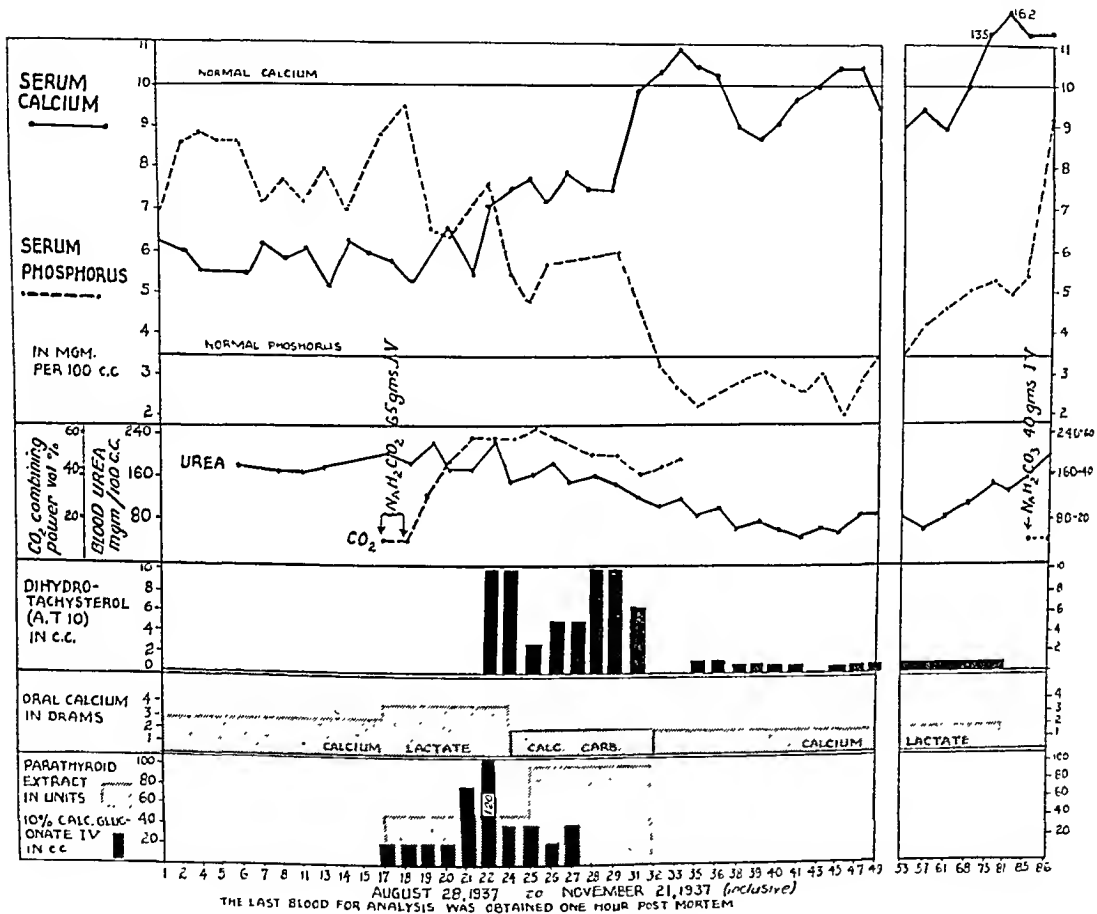
In the spring of 1937, the attacks began to assume the character of true tetany; there was carpopedal spasm as well as spasm of the neck, back, and leg muscles. Spasm of the muscles of the jaw was so marked that she could not open her mouth. Trousseau's and Chvostek's signs became positive.

She was admitted to the hospital on August 28, 1937, with fairly characteristic tetany attacks. The level of serum calcium was 6.2 mg., phosphorus 6.8 mg., and blood urea 180 mg. per 100 c.c. The urea clearance test showed 10 per cent clearance at the end of the first hour and 13 per cent at the end of the second. This was the first time significant evidence of kidney damage had been demonstrated. There was no steatorrhea. The erythrocyte count at that time was 4,520,000, with 81 per cent hemoglobin; the leukocyte count was 10,550, with 76 per cent polynuclears. The urine showed a strongly acid reaction, a faint trace of albumin, and was loaded with white cells. Roentgen studies of the skeleton showed no decalcification of the spine, ribs, or pelvis. Some improvement followed administration of vitamin D, parathyroid extract and calcium gluconate intravenously, and she was dismissed on September 4, 1937, 50,000 units of vitamin D being given daily.

Her course during the ensuing 9 days was progressively downhill, and she was readmitted to the hospital on September 13, 1937, apparently in a dying condition. She was semicomatose, the skin was flushed, and the respirations hyperpneic in character. Urea frost was present during the next few days. The level of serum calcium was 5.9 mg., phosphorus 8.9 mg. per 100 c.c., blood urea 207 mg. per 100 c.c., non-protein nitrogen, 123.2 mg. per 100 c.c., and carbon dioxide combining power 9.9 volumes per cent. A specimen of urine secured by catheterization on September 15 showed one plus albumin and it was loaded with white cells. Examination of the blood on September 21 showed 2,880,000 red cells with 58 per cent hemoglobin and 16,450 white cells with 83 per cent polymorphonuclears.

The important blood chemical findings from August 28 to November 21, the day of her death, may be traced on the accompanying chart. The days numbered 17 to 49 inclusive cover the period of this hospitalization. The output of urine was consistently high, varying as a rule between 2000 and 3000 c.c. per day with a relatively fixed specific gravity, the morning specimen never falling below 1.007 and never rising above 1.014. Her immediate danger was the severe acidosis which was successfully overcome by the intravenous administration of 65 grams of sodium bicarbonate (5 per cent solution) in two days. The tetany was treated first by parathyroid extract

given in doses of 50 units per day from the seventeenth to the twenty-fifth day and 100 units daily from the twenty-fifth to the thirty-second day. Calcium gluconate in 10 per cent solution was given in amounts varying from 20 to 120 c.c. daily from the seventeenth to the twenty-seventh day. These were followed by only a slight shift in calcium and phosphorus levels. Dihydratichysterol (A.T.-10)* was started on September 18, following which there was a striking return of the serum calcium and phosphorus to normal levels, as may be seen on the chart. Coincident with the improvement in serum calcium and phosphorus levels, the blood urea fell, being 68 on the day of dismissal from hospital (day 49 on the chart). A part of the improvement was judged to be due to glucose solution given intravenously each day and to



two blood transfusions. Cultures of the urine made shortly after admission showed *Bacillus proteus* on three occasions; all others showed *Bacillus coli* only. Urinary antiseptics included 20 c.c. of salihexin and 110 c.c. of prontasil. There was some improvement in the urine but small amounts of albumin and some pus were persistently present. The erythrocyte count and hemoglobin were only slightly increased. Urea clearance on dismissal was 19 per cent at the end of both the first and second hours. The improvement in blood chemistry was strikingly manifested by clinical improvement, and she was discharged on October 16. Doses of 2 c.c. of A.T.-10 were prescribed every second day and calcium lactate was given in doses of one-half a dram four times daily.

* A.T.-10 is a 0.5 per cent solution of dihydratichysterol ($C_{28}H_{46}O$) in oil of sesame. (Winthrop Chemical Co.)

The patient remained under observation at home from October 16 to November 20. During this time, although ambulatory, she rested a great part of each day and was extremely pale and weak. She had no further attacks of tetany. The levels of serum calcium and phosphorus were checked at intervals of four days to a week and remained essentially normal until November 16, when the calcium was found to be 16.2 mg. per 100 c.c. The use of dihydrotachysterol was discontinued at once. The blood urea gradually rose and on November 16 was 126 mg. per 100 c.c. An intravenous urogram made on this day showed no function of either kidney. She became progressively weaker during the ensuing four days and was again admitted to the hospital on November 20, 1937. At that time she was prostrated, her face was flushed, respirations were labored and hyperpneic, there was generalized muscular aching and tenderness. On admission, the carbon dioxide combining power was 10.9 volumes per cent, the blood urea 165 mg. per 100 c.c., and serum calcium 13.1 mg. per 100 c.c. The erythrocyte count was 4,040,000, hemoglobin 65 per cent and leukocyte count 15,700. The urine showed a trace of albumin and an occasional pus cell. She was given a total of 40 grams of sodium bicarbonate (5 per cent solution) and 1,000 c.c. of 10 per cent glucose in distilled water intravenously that evening. In spite of this, agonizing muscular pain developed which was only partially relieved by large doses of morphine, her temperature rose to 104° F. during the night, she sank into coma, and died early the following morning. In blood drawn about one hour post mortem, the urea was found to be 186 mg. per 100 c.c., serum calcium 13.0 mg. per 100 c.c., phosphorus 8.6 mg. per 100 c.c., and carbon dioxide combining power 10.9 volumes per cent.

At autopsy, the only significant findings were in the kidneys. The parathyroid glands were normal. The right superior parathyroid weighed 30 mg., the right inferior 60 mg., the left superior 55 mg., the left inferior 50 mg. There were no deformities of the urinary tract such as are so frequently seen in renal rickets of childhood. The following is a report by Dr. Allen Graham of the gross and microscopic renal pathology, the latter illustrated in the accompanying photomicrographs (figures 1 and 2).

"The right kidney weighs 115 gm. and the left 132 gm. Both are slightly smaller than normal and are covered by a thin capsule which strips fairly easily without tearing, leaving a fairly smooth surface, diffusely studded with minute white opaque areas. There are also diffuse, small cortical cysts in each kidney. Both kidneys cut with increased resistance. The cut surfaces are bulging and glistening. There is atrophy of the cortex throughout, and all the pyramids are considerably enlarged relatively and actually, and have a homogeneous, bluish white appearance. The papillae are considerably enlarged, somewhat edematous, but not ulcerated. There are a number of cysts involving the pyramids and the cortex, varying from 0.5 to 1.5 cm. in diameter. The calices, pelves, and ureters appear normal. There is a usual amount of peripelvic fat, which is not indurated. There is only a mild degree of atherosclerosis of the renal vessels." Postmortem cultures from both kidneys were negative and from both kidney pelves showed *Bacillus coli*.

Microscopic. "Sections from both kidneys show well marked arteriolar and glomerular sclerosis, extensive atrophy and degeneration of tubular epithelium, with considerable diffuse fibrosis in the cortex and very marked fibrosis in the pyramids. Many of the less affected tubules are considerably dilated. There are numerous areas of scarring in the cortex and considerable round cell infiltration in some areas. The large branches of the renal arteries show very little arteriosclerosis." (Figures 1 and 2.)

The pathologic diagnosis was, "bilateral, advanced, arteriolar nephrosclerosis, and chronic pyelonephritis."

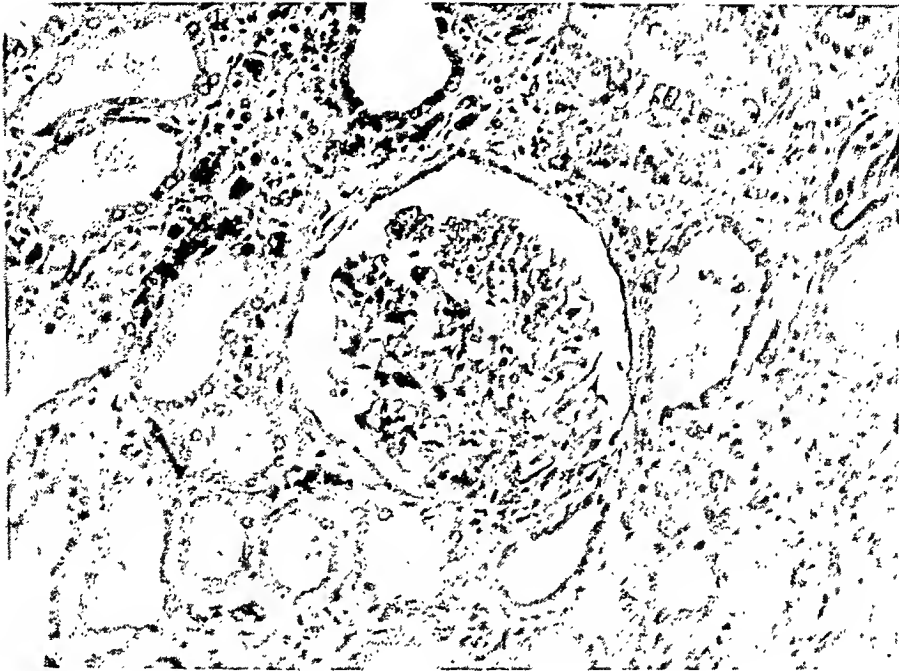
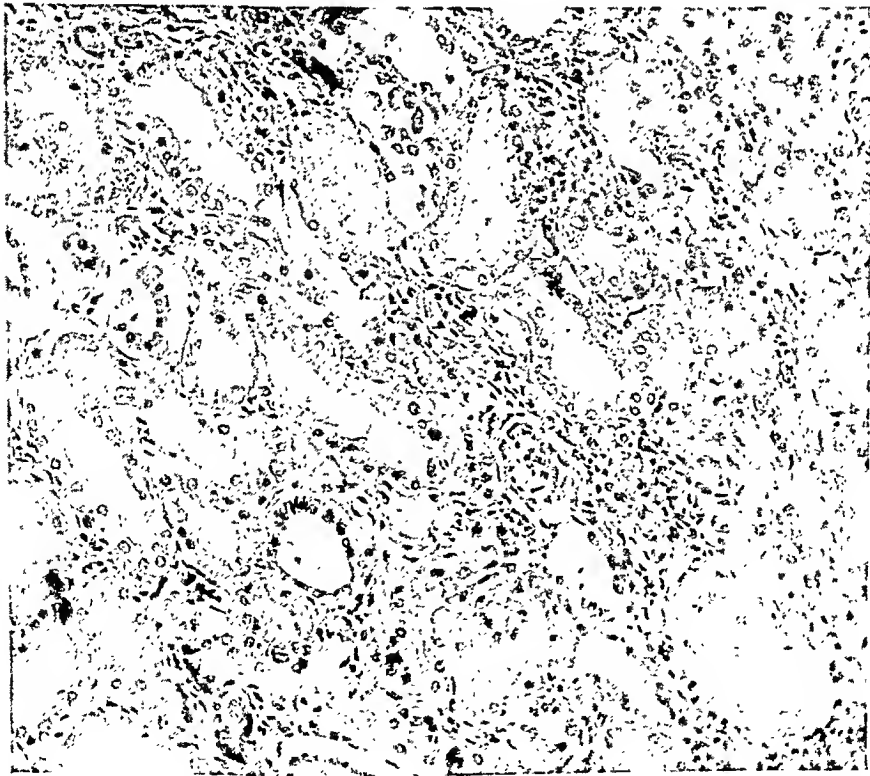
*A**B*

FIG. 1. *A*. Relatively unaffected glomerulus ($\times 150$). *B*. Degenerative changes in the convoluted tubules ($\times 150$).

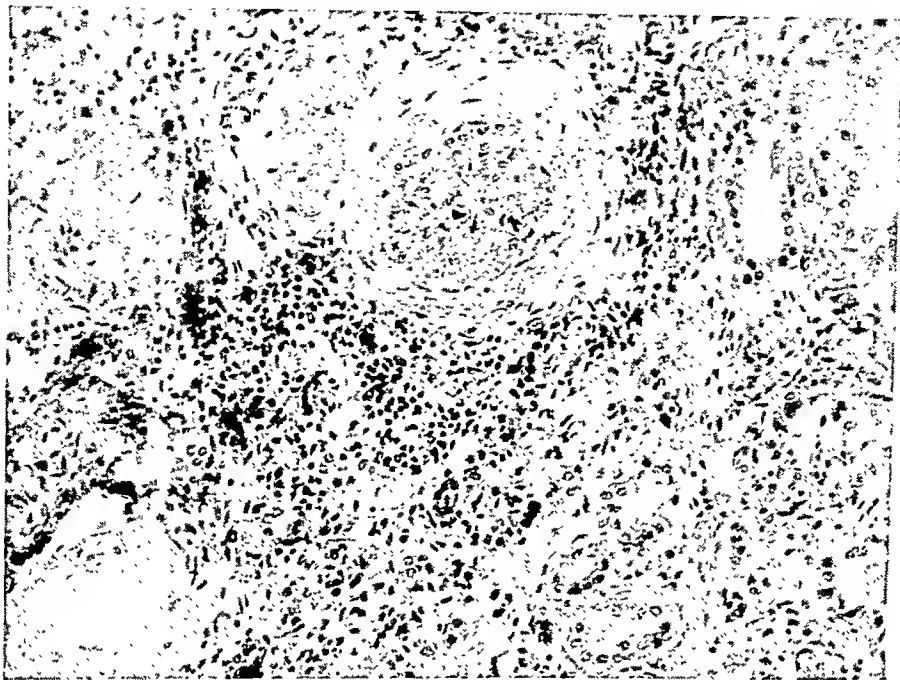
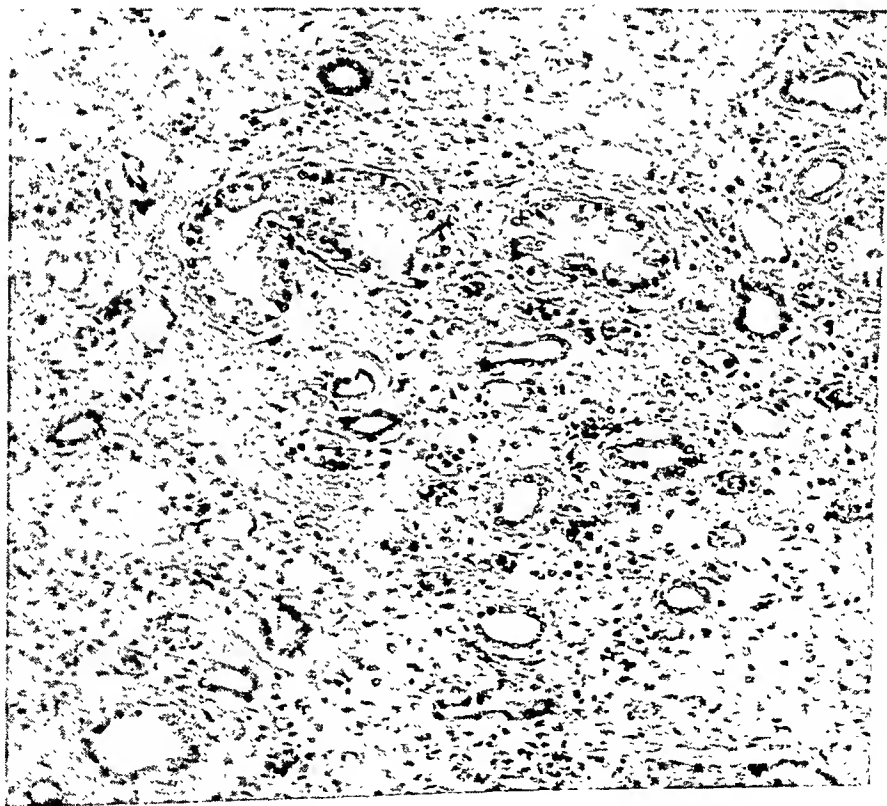
*A**B*

FIG. 2. *A*. Marked degree of arteriosclerosis, atrophy and fibrosis of parenchyma ($\times 150$). *B*. Extensive fibrosis of medulla with atrophy of tubules ($\times 150$).

COMMENT

This case is presented because of the rarity of tetany of renal origin in adults. It evidently simulates closely the changes seen with renal rickets in children. Spells of muscular flaccidity preceded signs of severe renal insufficiency by many years. Symptoms and signs typical of tetany appeared one and one-half years before death. The relative absence of urinary evidence of renal damage is consistent with the type of chronic pyelonephritis demonstrated and the complete absence of arterial hypertension is an interesting feature. No decalcification of the skeleton and no parathyroid abnormalities were recognized. The behavior of the serum calcium and phosphorus under the influence of dihydrotachysterol is demonstrated. The marked rise in the level of the serum calcium and fall of blood phosphorus, since they were persistent, could not be accounted for on the basis of intravenous calcium or parathyroid extract given. These levels had not responded to oral calcium therapy previously and were therefore due to the action of dihydrotachysterol. The lag between the time of first administration and the shift in serum calcium and phosphorus levels as well as the cumulative effect is typical of this drug.

APLASTIC ANEMIA TREATED WITH DAILY TRANSFUSIONS AND INTRAVENOUS MARROW; CASE REPORT *

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THIS case is of interest for several reasons. The disease is uncommon. This patient received 43 transfusions totaling almost 22 liters of blood in 52 days. This prolonged life but produced polycythemia and enlargement of the spleen. Despite the amount of blood transfused the leukocyte and platelet counts remained at a relatively low level. No record was found of so large an amount of blood being given within this space of time.

CASE REPORT

A white school girl, 19 years of age, entered Multnomah County Hospital on October 26, 1937, complaining of weakness, pallor, shortness of breath, and bleeding from the gums.

She had fibrocaceous tuberculosis of the apex of the right upper lobe since 1925. In 1931 she was treated for pleural effusion. She never had hemoptysis, cavitation, or tubercle bacilli in the sputum. She was found to be clinically well on examination at regular intervals from 1933 until about September 1937, when she first noticed dyspnea on exertion, pallor, and a throbbing sensation in her head. Her physician † gave her iron and liver extract and made the blood examinations recorded in table 1. On October 26, she first noticed slight bleeding from a spot on the gums near the left upper molars and black stools. She was sent then into Multnomah County Hospital.

* Received for publication August 27, 1938.

From the Department of Medicine, University of Oregon Medical School; and Multnomah County Hospital, Portland, Ore.

† The information on the illness from 1925 to Oct. 26, 1937, including the information in table 1, was kindly supplied by Dr. Ralph C. Matson of Portland, Oregon.

TABLE I
Blood Examinations Prior to Admission to Multnomah County Hospital

Date	Hemoglobin		R.B.C. millions per cu. mm.	W.B.C. per cu. mm.
	%	grams		
3/ 8/37.....	109	15.04	4.49	
10/ 4/37.....	39	5.38	2.55	
10/14/37.....	38	5.24	1.71	5,100
10/16/37.....	32	4.42	1.10	4,500
10/20/37.....	31	4.28	1.30	2,550
10/22/37.....	25	3.45	1.06	1,800
10/25/37.....	10	1.38	0.68	2,250

Careful questioning revealed no history of exposure to benzol, aminopyrine, arsphenamine, or other drugs containing the benzol ring. No exposure to radioactive substances was discovered. Between September 1931, and August 1937, she had 32 roentgenograms of the chest, and from October 13, 1933, until May 7, 1934, she had 59 five c.c. intravenous injections of gadusan, a preparation containing copper morrhuate. From May 9, 1934, to January 8, 1935, she was given 22 injections, intramuscularly, of oleosanocrysin which is gold sodium thiosulphate in oil. The individual injections varied from 0.1 to 0.5 gram, and totalled 5.4 grams.

Physical examination revealed a well nourished, well developed girl of asthenic habitus with an extreme white pallor. The temperature was 99.2° F. (37.3° C.), the pulse 130, and the respiration 22. The blood pressure was 110 systolic and 60 diastolic. The mucous membranes of the conjunctiva and mouth were almost white. There was one small bleeding point on the gums. Several fresh hemorrhages were noted in the retina of each eye near the disc. There were two small petechiae on the palate. There was slightly impaired resonance over the right apex but no râles or alterations in breath tones. There was no sternal tenderness, and the spleen, liver and lymph nodes were not enlarged to palpation. The fingernails were somewhat atrophic, but there was no spooning.

Laboratory studies established the diagnosis. The results of the blood examinations are given in tables 1 and 2. Table 3* gives the nearest equivalent to the terms here used for the cells of the granulocyte and erythrocyte series. Urobilinogen was absent from the urine, and one plus albuminuria was noted on one or two occasions. A sternal puncture on the day of admission revealed hemoglobin, 13 per cent (1.80 grams); akaryocytes, 0.44 million per cubic millimeter; nucleated cells, 725 per cubic millimeter; color index, 1.33; neutrophile lobocytes, 10 per cent; neutrophile rhabdocytes, 9 per cent; neutrophile metagranulocytes, 1.5 per cent; neutrophile granulocytes, 4.0 per cent; progranulocytes, 0.5 per cent; lymphocytes, 45 per cent; monocytes, 0.5 per cent; metakaryocytes and karyocytes, 27 per cent; karyoblasts, 0.5 per cent; disintegrating cells, 2.0 per cent.

The differential diagnosis, prior to the sternal puncture, included aplastic anemia, acute leukemia, and pernicious anemia. The sternal marrow findings definitely established the diagnosis of aplastic anemia with extreme normocytic anemia, thrombopenia, and leukopenia.

Pentose nucleotide, liver extract, blood transfusions, sodium perborate mouth wash, and intravenous sternal marrow injection were used therapeutically. The diet was high in protein with added brewer's yeast, viosterol, and orange juice to

* For the exact meaning of the terminology used here, consult Osgood, E. E., and Ashworth, Clarice M.: Atlas of hematology, 1937, J. W. Stacey, Inc., San Francisco.

TABLE II
Transfusions and Results of Blood Examinations

Date	Amt. of trans- fusion, c.c.	R.B.C. million per c.c.	Hb. grams	W.B.C. per cu. mm.	Reticu- locytes	N. Lobo- cytes, %	Lym- pho- cytes, %	Plate- lets	Hemor- rhage
10/26/37		0.94	3.48	3,800	1.0	27	63	16,000	++
10/27/37	550								
10/28/37	250								
10/29/37	500								
10/30/37	600	1.05	3.04	1,150	1.0	51	43	50,000	
10/31/37	500	1.50		1,000					
11/ 1/37	500	2.62	5.58	3,300	0.4	21	64	42,000	
11/ 2/37	600	3.20	8.13	3,900	1.4	14	74	140,000	
11/ 3/37	500								
11/ 4/37	500								
11/ 5/37	550	3.90	11.17	2,850	0.2	16	78	42,000	
11/ 6/37									
11/ 7/37	500								
11/ 8/37									
11/ 9/37	500	4.50	12.28	2,950	0.6	30	64		
11/10/37									
11/11/37	250								
11/12/37									
11/13/37	800	5.18	12.04	3,950	0.8	65	28	128,000	
11/14/37									
11/15/37		5.36	14.44	1,550	0.2	40	54	36,000	
11/16/37									++
11/17/37		5.06	15.97	1,550	N.F.	65	29	44,000	++
11/18/37									++++
11/19/37	500			1,000	N.F.	0	100	74,000	++++
11/20/37	600			1,250		20	80		++++
11/21/37	350	5.63	15.01	2,550		0	94		++++
11/22/37	600	4.45	12.70	750	N.F.	8	92	48,000	++++
11/22/37		4.35	12.09	1,400				20,000	++++
11/23/37	550	4.26	12.36	550	1.0	12	83	20,000	
11/24/37	500	4.57	12.86	850		6	92		
11/25/37	600								
11/26/37	500								
11/27/37	600	5.60	16.42	1,250	0.6	8	82	56,000	
11/28/37	600								++
11/29/37	500	5.10	15.57	1,750	N.F.	2	98	18,000	++++
11/30/37	500	5.35	17.49	1,650	N.F.	4	92	90,000	++++
12/ 1/37	350	5.44	16.12	1,150	0.8	8	92	42,000	++++
12/ 2/37	500								++++
12/ 3/37	500	5.81	17.47	1,050	0.6	24	72	36,000	++++
12/ 4/37	100								++++
12/ 5/37	575								++++
12/ 6/37	650 (-750)	8.11	18.00	280	0.2	6	84	112,000	++++
12/ 7/37	500	5.70	15.69	230	N.F.	0	94	96,000	++++
12/ 8/37	600	5.05	13.04	1,100	N.F.	6	90	58,000	++++
12/ 9/37	400	5.42	14.25	1,550	0.6	2	94	124,000	++++
12/10/37	600	5.08	11.73	1,050				90,000	++++
12/11/37	500								++++
12/12/37	500								++++
12/13/37	575+18	c.c. sternal marrow							++++
12/14/37	500	5.13	11.87	1,000		0	98	56,000	++++
12/15/37	500	4.45	10.91	750		0	98	50,000	++++
12/16/37	600	4.50	10.91	300		4	96	68,000	++++
12/17/37	420	3.80	9.66	250		8	80	70,000	++++

TABLE III
Nomenclature

Terms here used	Nearest equivalent
Lobocyte.....	Polymorphonuclear
Rhabdocyte.....	Staff cell
Metagranulocyte.....	Metamyelocyte
Granulocyte.....	Myelocyte
Progranulocyte.....	Promyelocyte
Granuloblast.....	Myeloblast
Akaryocyte.....	Non-nucleated erythrocyte
Metakaryocyte.....	Normoblast
Karyocyte.....	Pronormoblast
Prokaryocyte.....	Erythroblast
Karyoblast.....	Megaloblast

insure an adequate vitamin intake. Pentose nucleotide was given in 10 c.c. doses, intramuscularly, twice daily on October 27 and 28. Unconcentrated liver extract was given intramuscularly in doses of 3 c.c. twice a week until November 18. Sodium perborate mouth wash was used at frequent intervals, and sodium perborate paste was applied to the gums following meals. As shown in table 2, a total of 43 transfusions and 21,870 c.c. of blood were given by the citrate method. On December 13, 18 c.c. of sternal marrow were obtained from her brother, a compatible donor. This was introduced into marrow culture medium,² thoroughly mixed, added to 500 c.c. of blood obtained from the same donor, and injected slowly intravenously. No reaction occurred.

At first the course of her illness was surprisingly favorable. The bleeding ceased after the first transfusion and did not recur until November 16. The course of the temperature, pulse, and respiration are shown in chart 1, and of the blood examinations in table 2. She was afebrile, except for a slight elevation of the temperature after the second, third and fifth transfusions, until November 13 when she contracted a typical acute follicular tonsillitis from another patient. There was no evidence of gangrenous stomatitis. The follicular tonsillitis had cleared up by November 20, but fever persisted and became continuous in character after November 18. Bleeding occurred as indicated in table 2. On November 24, an abscess on the right buttock was discovered at the site of injection of liver extract which later became fluctuant and was drained. *Staphylococcus aureus* was recovered from the pus. A second sternal puncture on November 23 revealed hemoglobin, 110.0 per cent (15.32 grams); red blood cells, 4.36 million; nucleated cells, 1,150; neutrophile lobocytes, 8.4 per cent; neutrophile rhabdocytes, 0.4 per cent; lymphocytes, 83.6 per cent; prolymphocytes, 0.4 per cent; eosinophile lobocytes, 0.8 per cent; monocytes, 0.4 per cent; disintegrated cells, 6.0 per cent. By December 6, the red cell count exceeded 8 million. Since the leukocyte count was only 280, 750 c.c. of blood were withdrawn from her vein to allow further transfusion. From December 7 on, the increased fever and pulse rate, and the increasing dyspnea and cyanosis without other apparent cause led to consideration of miliary tuberculosis. Blood cultures were negative. By December 15, the cyanosis was extreme. The patient developed jaundice which was apparently of hematogenous origin. She died December 18.

The final diagnosis was normocytic anemia "corrected"; leukopenia and thrombopenia from complete aplasia of the bone marrow of undetermined etiology; multiple hemorrhages into the viscera and from the mucous membranes; terminal bronchopneumonia; old healed fibroid tuberculosis of the right upper lobe and apex of the left lower lobe; possible miliary tuberculosis of pulmonary type; splenomegaly with evidence of blood destruction; generalized icterus of hematogenous origin; staphylococcus abscess of the right buttock.

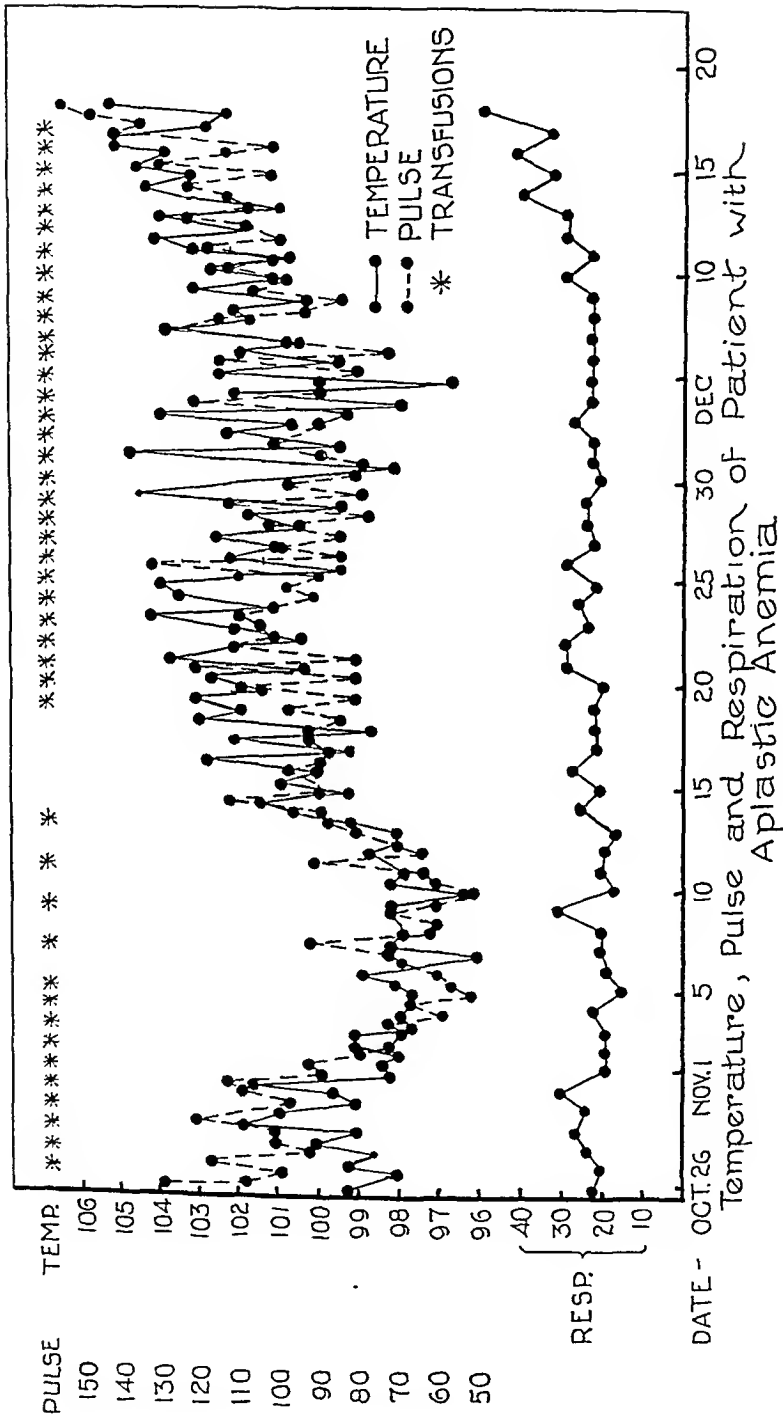


CHART 1.

Necropsy: Necropsy was performed* on the day of her death. The abscess on the buttock was healed, but a decubitus ulcer, measuring 3 by 2 cm., was present over the sacral promontory. The significant findings aside from petechiae in the serous membranes were in the marrow, lungs, spleen, and liver. There was no enlargement of the superficial or deep lymph nodes. Grossly, the ribs, sternum, and vertebral bodies revealed a markedly porous appearance with almost complete absence of marrow. The visceral and parietal pleura of the right lung were adherent by dense fibrous adhesions. On section the right lung was markedly bloody, consolidated, heavy and devoid of air. The section of the left lung revealed a dependent hypostasis with consolidation. The spleen was markedly enlarged, weighing 450 grams and measuring 17 centimeters in length, 10 centimeters in breadth, and 6 centimeters in thickness. The capsule was thick and grayish-black in color. The cut surface was bloody in appearance, purple to black in color, and had a fairly thin pulp. The liver was large, weighing 1,800 grams and showed petechiae beneath the capsule.

Microscopic examination of these tissues revealed findings of great interest. The marrow (figure 1) consisted largely of fat, but occasional islets of regenerating marrow which appeared essentially normal were visible. Sections from the apex of the right lung revealed extensive areas of fibrosis, infiltrated with focal collections of lymphocytes. There was a single large area of caseation necrosis surrounded by intact epithelioid cells and lymphocytes and an adjacent small active "daughter tubercle." Most of the substance of the lung in this region was made up of dense scar tissue. Many of the alveoli contained large numbers of monocytes filled with hemosiderin. There was extensive intra-alveolar hemorrhage. Sections of cut parts of the lungs revealed a patchy pneumonia which had become organized. The exudate contained monocytes and fibroblasts but no neutrophils. In most sections of both lungs, thrombi were noted within the pulmonary vessels which were partially organized, and contained large clumps of cocci, some in chains and others diplococci. In some areas the bacteria were found in the surrounding parenchyma as well as within the vessels. There was no cellular reaction about these clumps of bacteria. No organisms were noted in any other tissue except the lungs. Sections of the spleen revealed large amounts of blood pigment. There was a good deal of phagocytosis of this pigment but no evidence of hematopoietic activity. Very few leukocytes were present. In sections of the liver the K  pfer cells contained large amounts of hemosiderin.

The anatomic diagnosis was terminal bronchopneumonia, bilateral, with multiple bacterial emboli in the pulmonary arterioles; aplastic anemia; hemorrhages into pelves of the kidneys, the mucosa of the stomach, and beneath the capsules of the kidneys and liver; hypoplastic bone marrow; old healed fibroid tuberculosis, right lung; generalized icterus; chronic passive congestion of the spleen and kidneys; splenomegaly; chronic fibrous obliterative pleuritis, complete, right lung; cystic endocervicitis; decubitus ulcer; hematomata in both cubital fossae of the arms.

COMMENT

The etiology of the aplastic anemia in this case is not definitely established, although the patient had been exposed to two known causes of this disease, gamma radiation³ and gold sodium thiosulphate.⁴ Since the chest roentgenograms were taken over a period of seven years, it does not seem possible that this small amount of radiation could account for her illness. Aplastic anemia has been produced by smaller amounts of gold preparations than she received. It seems unlikely, however, that it was the cause in this case because the last dose of gold was given in 1935, more than 19 months before the onset of the

* Drs. Warren C. Hunter and Bernard F. Ryan of the Pathology Department of the University of Oregon Medical School performed the necropsy.

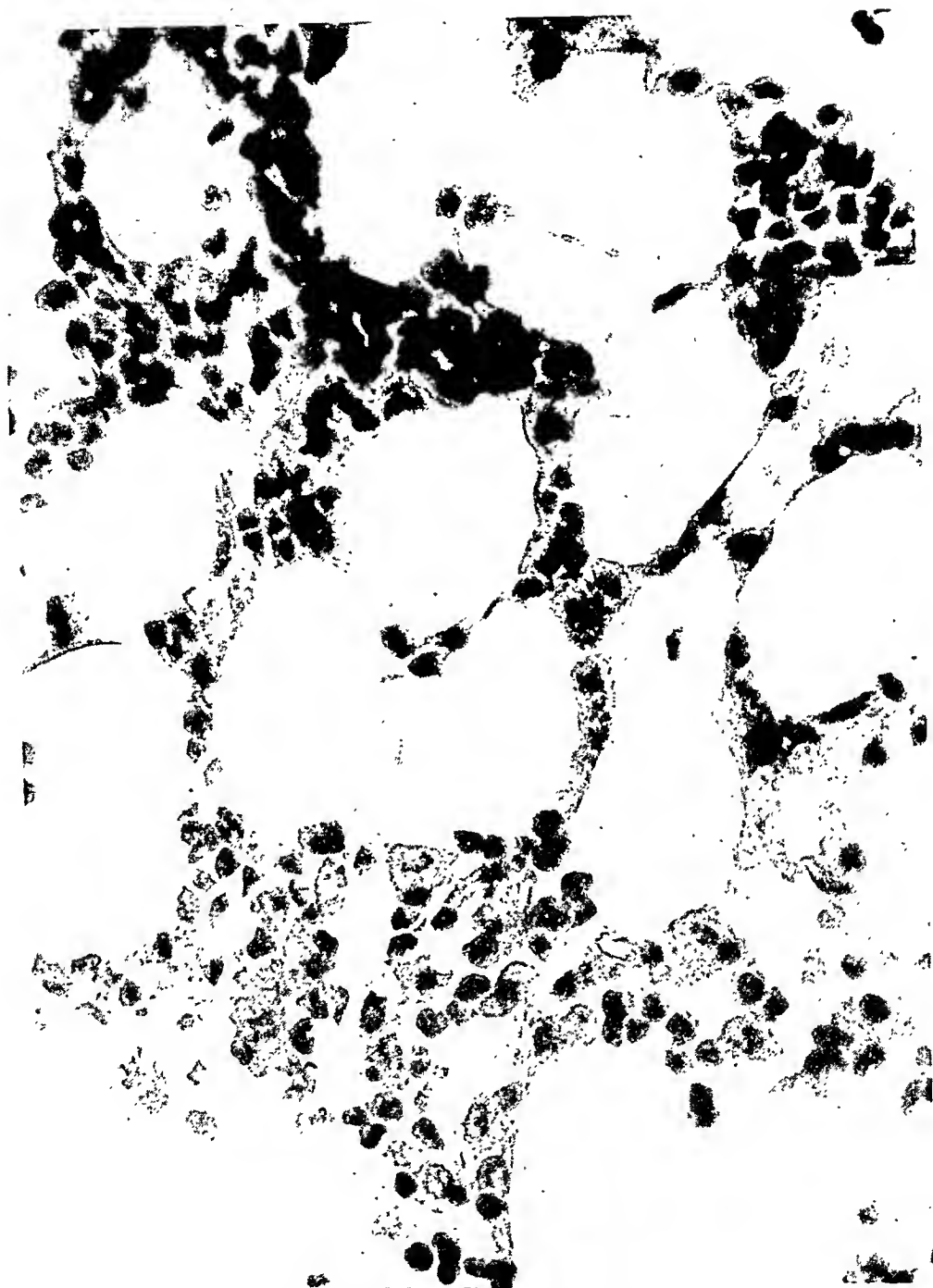


FIG. 1. Photomicrograph $\times 800$ of Giemsa stain of rib marrow from the patient with aplastic anemia, obtained at necropsy. Note the aplasia with beginning islets of regeneration.

symptoms. In most of the reported cases of aplastic anemia from gold the symptoms have begun within one month of cessation of treatment. Many cases of "idiopathic" aplastic anemia have been recorded, but since the introduction of the sternal puncture method⁵ of studying marrow, it has been learned that many cases with this blood picture are actually cases of aleukemic or subleukemic leukemia. In most of the patients with a truly aplastic marrow⁶ a definite cause such as exposure to benzol, benzol ring drugs, gamma, alpha or beta radiation, can be found. Another rare cause of aplastic anemia is the end-stage of certain cases of lymphocytic leukemia.⁷ The authors have recently seen a patient belonging to this group who was admitted to Multnomah County Hospital in August 1937, with enlargement of the spleen and lymph nodes, petechiae in the skin, and a sternal marrow showing a great increase in lymphocytes with many prolymphocytes and lymphoblasts. This patient refused treatment and left the hospital but returned in June 1938, a few hours before he died. A complete necropsy with careful examination revealed no evidence of leukemia, whatsoever, and typical aplastic marrow. The spleen was no longer enlarged, and it seems certain that had this patient been seen only on his last admission, he would have been classified as "idiopathic" aplastic anemia. Lymphocytic leukemia with terminal aplasia can be excluded here because of the long period of observation before the onset of this patient's anemia. The combination of benzol ring drugs and low vitamin B₁ intake⁸ can be excluded because her previous diet was high in vitamin content, and there was no history of administration of benzol ring drugs and no response to a high vitamin B₁ intake. It must be concluded that the etiology in this patient is not known although delayed absorption of gold salts from the oily suspension can not be excluded.

The transfusions were given daily for definite reasons. It has been shown⁹ that in patients and animals with aplastic anemia due to benzol poisoning or excessive gamma ray exposure the marrow will eventually regenerate if they survive. From the clinical condition of the patient when first seen and the extreme depletion of the erythrocyte, granulocyte, and thrombocyte series in both the bone marrow and the blood, it seemed unlikely that she could live more than a few days without transfusions to supply all of these three types of cells essential for her survival. It has been shown¹⁰ that neutrophile lobocytes live only about 48 to 90 hours, and the duration of life of the platelets is thought to be rather short. Since one transfusion represents only about one-tenth of the volume of the patient's blood, one could hope to increase the level of a particular cell type by only about one-tenth of the concentration in the donor's blood. It can readily be calculated from these data that transfusions to maintain life with relatively complete aplasia of the marrow must be given at frequent intervals. Since the duration of life of the akaryocytes has been variously estimated at from 30¹¹ to 80¹² days, it is evident that if enough transfusions are given to maintain a sufficient number of neutrophiles and platelets to sustain life, a polycythemia will ultimately develop, as occurred in this case. Splenomegaly with active phagocytosis and rapid destruction of akaryocytes developed in this patient, apparently as a compensatory mechanism. This simulated closely the pathology in the spleen and liver in polycythemia rubra vera and suggested that the changes in the spleen and liver in this disease may be purely secondary. The possibility of separating the platelets and leukocytes from the

akaryocytes by fractional centrifugation was considered. The danger of introducing infection by the extra manipulations out-weighed the advantages. Eventually, it is hoped that marrow culture technic² may lead to the development of pure cultures of cell types for use in these conditions. Bleeding as a method of controlling the polycythemia was decided on as a safer and simpler procedure.

Because of the relatively complete aplasia of the marrow and the relative freedom from hemorrhage, it seemed possible that the duration of life of the akaryocytes might be calculated from the data on the amounts of blood transfused and the counts at intervals, thereafter. However, counts were not made on the donor's bloods, and the errors in the measurement of the volume of blood transfused, in the estimation of the patient's blood volume, and in the estimation of the donor's blood counts on the basis of normals, are too numerous and cumulative to justify such calculations. The erythrocyte counts up to November 21 fit very well with the counts calculated on the basis of a duration of life of the akaryocytes of 40 days if it is assumed that 500 c.c. represents one-tenth of the patient's blood volume, and that the donors had an average akaryocyte count of 5.0 million. Studies with the technic of marrow culture¹⁰ offer promise of a much more accurate solution of this problem.

There were several reasons for administering sternal marrow intravenously in the manner employed. It seemed possible that in complete aplasia of the marrow there might be no remaining cells from which new marrow could develop. Intrasternal injection of marrow had been tried by one of us (E. E. O.) in another patient with aplastic anemia, and it had been found to be impossible to inject, apparently because collapse of the sinuses acted as a valve preventing egress of blood to make space for the injected marrow. Even if intrasternal injection of marrow were successful, it seems doubtful whether an adequate blood supply to the central areas of the injected material would be developed before necrosis had occurred. It is known that a small number of immature cells of the marrow are present even in normal blood, and it seems possible that the development of hyperplastic marrow in areas of normally fatty marrow may normally occur by means of blood stream metastasis.

The chief danger of intravenous marrow injection was considered to be fat embolism. For that reason, the marrow was first mixed with a considerable volume of blood from the same donor, and then very thoroughly mixed, with the hope that some of the free fat would be held in solution or suspension by the usual mechanisms of blood plasma for carrying fat. The absence of any evidence of a reaction in this patient would indicate that this procedure was successful. The donor chosen was a relative and of the same blood group (A) with the thought that such marrow might be more likely to survive than marrow from another donor. There is no evidence in this case that the marrow injection was effective. It apparently did no harm. It is possible that the regenerating islets in the marrow at the time of death were developed from the injected marrow cells, but there is no way of proving this. Certainly, the immature cells disappeared from the blood quickly. No foci of hematopoiesis were found outside of the marrow at necropsy. However, this could have been accounted for by destruction of the cells as well as by their localization in the marrow.

In this patient the injection of marrow was delayed until all hope from

other methods of therapy seemed gone because it was a new procedure. It would seem justifiable to try this method of therapy earlier next time in view of the seriousness of the disease, the logic underlying the therapy, and the absence of untoward reactions in this patient.

The extreme susceptibility of patients with aplastic anemia to infection is well known. This case illustrates the importance of efforts to guard these patients from every possible source of infection. Sodium perborate was used locally in the mouth, and transfusions were given to combat infection of the mucous membranes which commonly develops when the neutrophile lobocytes in the blood are markedly decreased in number. This infection which occurs in agranulocytosis and acute or subacute leukemia as well as in aplastic anemia appears to result from invasion by organisms already present in the mouth. In our experience, transfusions to provide the necessary number of granulocytes combined with sodium perborate to supply the additional peroxidase usually prevents such infections. Since the absolute neutrophile count only once exceeded 100 per cu.mm. after November 22, it seems likely that the perborate prevented stomatitis in this case.

It is noteworthy that the major drop in neutrophiles occurred from November 17 to November 21, in the period immediately following omission of five transfusions on November 14 to 18.

The abscess on the buttock would not have developed if no intramuscular preparations had been given. Neither pentose nucleotide nor liver extract had any apparent effect.

The acute streptococci follicular tonsillitis might have been prevented by isolation. Possibly this tonsillar infection was the source of the infection in the lungs, especially in view of the studies of Larsell, Veazie, and Fenton,¹³ showing that infection from the sinuses and tonsils reaches the lungs by the route of the lymphatics and veins. This intravascular infection found at necropsy in the lungs undoubtedly explains the group of symptoms which were thought to be due to miliary tuberculosis, and accounts for the rapid downward course in the last week of life. It preceded the injection of sternal marrow so could hardly have been due to infected fat emboli. It also seems possible that she might have recovered had not this infection supervened in view of the beginning regeneration in the marrow and her relatively good condition until the onset of this infection.

The terminal bronchopneumonia, while probably the immediate cause of death, was similar to that which occurs in any patient who is moribund from any cause.

A number of lessons may be drawn from this case. Transfusions may be necessary daily or oftener in patients with complete aplasia of the bone marrow. In such patients omission of transfusion before marrow regeneration is well advanced may be disastrous. The frequency of transfusion depends on the necessities of each patient. Earlier intravenous injection of sternal marrow deserves further experimental trial. Patients with this disease should be carefully protected from every source of infection.

SUMMARY

A patient with aplastic anemia lived 53 days after admission to the hospital in extremis. She died as a result of intercurrent infection. She received

43 transfusions, totalling 21,870 c.c. of blood within a period of 52 days. So far as we can determine, this is the largest amount of blood ever transfused into one person in this period of time. Sternal marrow was administered intravenously without untoward reaction.

REFERENCES

1. OSGOOD, E. E.: A textbook of laboratory diagnosis, Ed. 2, 1935, P. Blakiston's Son and Company, Philadelphia, pages 397-403.
2. OSGOOD, E. E., and BROWNLEE, INEZ E.: Culture of human marrow: details of a simple method, *Jr. Am. Med. Assoc.*, 1937, cviii, 1793-1796.
3. SELLING, LAURENCE, and OSGOOD, E. E.: The action of benzol, roentgen-rays and radioactive substances on the blood and blood-forming organs, *Downey's Handbook of Hematology*, 1938, Paul B. Hoeber, Inc., New York, p. 2716.
4. DAMESHEK, WILLIAM: Aplastic anemia following treatment of lupus erythematosus with gold sodium thiosulphate; with a review of the literature of hematological reactions following gold therapy, *New England Jr. Med.*, 1934, ccx, 687-692.
5. ARINKIN, M. I.: Methodology of examining bone marrow in live patients with hematopoietic diseases, *Vestnik khir.*, 1927, x, 57.
YOUNG, R. H., and OSGOOD, E. E.: Sternal marrow aspirated during life: cytology in health and in diseases, *Arch. Int. Med.*, 1935, lv, 186-203.
VOGEL, P., ERF, L. A., and ROSENTHAL, N.: Hematological observations on bone marrow obtained by sternal puncture, *Am. Jr. Clin. Path.*, 1937, vii, 436.
6. ROSENTHAL, N.: Aplastic anemia and osteosclerosis, *Downey's Handbook of Hematology*, 1938, Paul B. Hoeber, Inc., New York, p. 2203.
7. MINOT, G. R.: Discussion of RHOADS, C. P., and BARKER, W. H.: Refractory anemia: Analysis of 100 cases, *Jr. Am. Med. Assoc.*, 1938, cx, 794-796.
8. RHOADS, C. P., and MILLER, D. K.: Effect of diet on susceptibility of canine hematopoietic system to damage by amidopyrine, *Proc. Soc. Exper. Biol. and Med.*, 1937, xxxvi, 654-656.
9. SELLING, LAURENCE: Benzol as a leucotoxin: studies on the degeneration and regeneration of the blood and haematopoietic organs, *Johns Hopkins Hosp. Rep.*, 1916, xvii, 83-142.
10. OSGOOD, E. E.: The histogenesis, classification and identification of the cells of the blood and marrow based on cultures and hematologic studies of human marrow and blood, *Am. Jr. Clin. Path.*, 1938, viii, 59-74.
11. ASHBY, W.: The determination of the length of life of transfused blood corpuscles in man, *Jr. Exper. Med.*, 1919, xxix, 267-281.
12. WIENER, A. S.: Longevity of the erythrocyte, *Jr. Am. Med. Assoc.*, 1934, cii, 1779-1780.
13. LARSELL, OLOF, VEAZIE, LYLE, and FENTON, R. A.: Streptococcic infection of the lungs from paranasal sinuses: experimental study, *Arch. Otolaryngol.*, 1938, xxvii, 143-150.

EDITORIAL

EQUINE ENCEPHALOMYELITIS IN MAN

The demonstration of the occurrence of equine encephalomyelitis in man adds another to the long list of human virus diseases. It also gives new interest and practical significance to some recent observations bearing on the epidemiology of this disease. It was first recognized by Meyer and his associates¹ in 1930 in a serious epizootic among horses in California. These observers isolated the virus from several animals in the earliest stages of the disease, and differentiated it from the other known viruses. They reproduced the disease in mice, rats, rabbits, monkeys, and most easily in guinea pigs, which were susceptible not only to intracerebral but also to intraperitoneal, intracutaneous and intranasal inoculation. They observed what they thought to be three cases of the disease in man but did not obtain direct proof of the presence of the virus in these cases.

In 1932 a similar disease was observed in horses in New England and the Atlantic states by Ten Broeck and Merrill² and others.³ These workers isolated a virus which was serologically distinct from that which Meyers had obtained in California. This virus, which is designated as the Eastern type of equine encephalomyelitis, is even more virulent than the Western type, causing a mortality of about 90 per cent among the horses attacked.

In 1938 during an extensive epizootic of the Western type of infection among horses in Minnesota, Eklund and Blumstein⁴ reported six cases of encephalitis with two deaths among farmers who had been in contact with diseased animals. One case which came to autopsy showed lesions in the central nervous system quite similar to those observed in animals. The virus was not isolated from any of these cases, but blood serum from one patient who recovered protected animals effectively from infection with the Western type of encephalomyelitis virus.

In 1938 another extensive outbreak of the Eastern type of encephalomyelitis occurred among horses in New England. Simultaneously cases of human encephalitis also appeared in the same localities. Feemster and his associates⁵ made a study of 38 such cases, of which 25 were fatal. All but one were children and most of them were under ten years of age. The Eastern type of equine encephalomyelitis virus was recovered from the brain

¹ MEYER, K. F.: A summary of recent studies on equine encephalomyelitis, *ANN. INT. MED.*, 1932, vi, 645.

² TEN BROECK, C., and MERRILL, M. H.: Serological difference between eastern and western equine encephalomyelitis virus, *Proc. Soc. Exper. Biol. and Med.*, 1933, xxxi, 217-220.

³ SHAHAN, M. S., and GILTNER, L. T.: Some aspects of infection and immunity in equine encephalomyelitis, *Jr. Am. Vet. Med. Assoc.*, 1934, lxxxiv, 928-934.

⁴ EKLUND, C. M., and BLUMSTEIN, A.: The relation of human encephalitis to encephalomyelitis in horses, *Jr. Am. Med. Assoc.*, 1938, cxi, 1734-1735.

⁵ FEEMSTER, R. F.: Outbreak of encephalitis in man due to the eastern virus of equine encephalomyelitis, *Am. Jr. Pub. Health*, 1938, xxviii, 1403-1410.

in eight cases by Fothergill et al.⁶ and by Webster and Wright.⁷ In seven other cases typical pathological lesions were found in the brain at autopsy. In four cases who recovered, a high degree of protective power for the Eastern type of virus was demonstrated in the blood. In one instance virus from a human source on intracerebral inoculation into horses produced the disease in one normal horse and in one immunized to the Western type of virus, whereas a horse immune to the Eastern type could not be infected.⁸

Quite recently Fothergill et al.⁹ have reported a fatal accidental infection in a laboratory worker, from whom the Western type of virus was recovered.

The clinical course of the disease in man^{5, 10} was characterized by a sudden onset with fever, irritability or drowsiness, often vomiting, headache and dizziness in older children, rigidity of the neck, cyanosis, muscular twitchings, convulsions and coma. Abnormalities of the reflexes were common but variable. Paralyses were occasionally observed. There was a polymorphonuclear leukocytosis. The cerebrospinal fluid was under increased pressure (200 to 350 mm. of fluid), was hazy, and showed from 200 to 2,000 cells per cu. mm. In the early stages from 60 per cent to 90 per cent of the cells were polymorphonuclear leukocytes, but in the later stages mononuclear cells predominated. The protein was much increased, the sugar usually normal.

Those who survived the acute stage often showed coma and muscular rigidity for a protracted period. Some patients who were thought to be cases of this infection recovered completely, others showed paralyses, mental disturbances or other permanent sequelae.

The brain in fatal cases, like that of experimental animals, showed edema and congestion, perivascular infiltration with leukocytes and plasma cells, some degree of cellular infiltration of the meninges, thrombi in the small vessels and focal areas of necrosis and infiltration.

These observations prove that man is susceptible to both the Eastern and Western types of the virus. The disease, at least in cases of obvious infection, runs a rapid course and has a high mortality. It differs clinically as well as serologically from the ordinary epidemic encephalitis, both of the Economo and St. Louis types.

The means by which the disease is spread are not known. In the case of the Massachusetts epidemic, contact with diseased animals could not be established. The incidence of the disease among horses does not favor the

⁶ FOTHERGILL, L. D., DINGLE, J. H., FARBER, S., and CONNERLY, M. L.: Human encephalitis caused by the virus of the eastern variety of equine encephalomyelitis, *New England Jr. Med.*, 1938, ccxix, 411.

⁷ WEBSTER, L. T., and WRIGHT, F. H.: Recovery of eastern equine encephalomyelitis virus from brain tissue of human cases of encephalitis in Massachusetts, *Science*, 1938, lxxxviii, 305.

⁸ SCHOENING, H. W., GILTNER, L. T., and STRAHAN, M. S.: Equine encephalomyelitis produced by inoculation of human encephalitis virus, *Science*, 1938, lxxxviii, 410.

⁹ FOTHERGILL, L. D., HOLDEN, M., and WYCKOFF, R. W. G.: Western equine encephalomyelitis in a laboratory worker, *Jr. Am. Med. Assoc.*, 1939, cxiii, 206-207.

¹⁰ WESSELHOEFT, C., SMITH, E. C., and BRANCH, C. F.: Human encephalitis. Eight fatal cases, with four due to the virus of equine encephalomyelitis, *Jr. Am. Med. Assoc.*, 1938, cxi, 1735-1741.

theory of contact infection, and this has not been accomplished experimentally. The seasonal occurrence of the disease in horses during the summer and autumn with complete cessation during the winter suggested some biting insect as the vector. It was shown by Kelser¹¹ and later by Merrill and Ten Broeck¹² that the infection can be conveyed to guinea pigs by the bites of *Aedes aegypti* and of several other species of *Aedes* mosquitoes. The virus was found in the legs and body fluids of infected insects. However, no naturally infected mosquitoes have yet been found. The infection was not conveyed through the egg to the next generation, nor could it be transmitted to the female by the male. Furthermore the experimental transmission in their hands was difficult and uncertain unless the mosquito, after it had engorged, was injured by pricking the abdomen with a sharp needle. Transmission of the Eastern type of virus by biting was accomplished only once. It seems likely, therefore, that some other variety of arthropod is the usual vector.

There is considerable evidence also that the horse is not an important reservoir of the virus. The mortality among horses with clinical manifestations of the disease is very high (50 to 90 per cent), and the disease runs a rapid course. Furthermore the virus can be demonstrated in the blood only for a very brief period in the initial febrile stage of the infection before clinical symptoms are manifest. In a few cases virus has been recovered from the blood of horses naturally infected although no manifestations of illness other than fever ever appeared. A few horses have been found (about 15 per cent of those examined from infected areas), whose serum showed protective power although no previous illness had been recognized.¹³ It is therefore possible for an animal to recover from the infection without developing encephalitis, but this appears to be uncommon. The possibility that the virus can maintain itself in horses seems remote.

As early as 1935 birds were suspected as being the reservoir host, partly because of the very wide range, yet sparse distribution of the disease along the Eastern coast.¹³ Investigations both in Europe and America have shown that many different species of birds are susceptible to inoculation with the virus (pigeons, chickens, ducks, geese, storks, vultures, European blackbirds, barriers, etc.). Confirmatory evidence for this theory was furnished by Tyzzer, Sellards and Bennett¹⁴ in 1938, who recovered the Eastern type of virus from the brains of four ring necked pheasants which were discovered paralyzed and moribund on a range in Connecticut. At about the same time Fothergill and Dingle¹⁵ obtained the virus from the brain of

¹¹ KELSER, R. A.: Mosquitoes as vector of the virus of equine encephalomyelitis, Jr. Am. Vet. Med. Assoc., 1938, xcii, 195.

¹² MERRILL, M. H., and TEN BROECK, C.: The transmission of equine encephalomyelitis by *Aedes aegypti*, Jr. Exper. Med., 1935, lxii, 687-695.

¹³ TEN BROECK, C., HURST, E. W., and TRAUB, E.: Epidemiology of equine encephalomyelitis in the eastern United States, Jr. Exper. Med., 1935, lxii, 677-685.

¹⁴ TYZZER, E. E., SELLARDS, A. W., and BENNETT, B. L.: The occurrence in nature of "equine encephalomyelitis" in the ring-necked pheasant, Science, 1938, lxxxviii, 505-506.

¹⁵ FOTHERGILL, L. D., and DINGLE, J. H.: A fatal disease of pigeons caused by the virus of the eastern variety of equine encephalomyelitis, Science, 1938, lxxxviii, 549-550.

a pigeon found dead in an infested area in New England. If the search for cases of spontaneous infection in migratory birds proves successful, as now seems probable, this will go far toward establishing this view that birds constitute the natural host for the virus. The horse and man appear to be merely accidental hosts, and are attacked only when conditions are especially favorable for the propagation of the infection. If this proves to be true, the term "equine" is obviously a misnomer.

Manifestly a great deal more work must be done before these problems are definitely solved. Enough is known, however, to indicate that the disease has become a serious public health problem, and that physicians should be alert to recognize the disease when it occurs.

P. W. C.

Erratum: In the article on "Visualization of the Chambers of the Heart and the Thoracic Blood Vessels in Pulmonary Heart Disease; a Case Study," by Dr. George P. Robb and Dr. Israel Steinberg, the legend (except for the figure number) given for figure 6 (page 26) should appear with figure 7 (page 28); likewise the legend appearing under figure 7 should be with figure 6.

REVIEWS

Clinical Gastroenterology. By HORACE WENDELL SOPER, M.D. 314 pages; 25.5 × 17.5 cm. C. V. Mosby Co., St. Louis, Missouri. 1939. Price, \$6.00.

Textbooks and monographs are often written in a very impersonal manner, and they may present facts in a way that makes uninteresting reading. This is not true of Dr. Soper's book. He has the ability to write medical literature that seems to be alive.

This volume is concerned primarily, as its title implies, with the clinical aspect of gastroenterology. It is in no sense a reference book but is essentially a record of the experiences of the author, and in the discussions, emphasis is placed on the methods that Dr. Soper has found to be most satisfactory. One may not agree entirely with all of his views, but this does not detract from the inherent usefulness of the book. There are placed at the end of each chapter numerous, well selected roentgenograms. These add greatly to a better understanding of the text.

It is a book to be used by anyone who would like to know how another individual would handle a certain problem in gastroenterology. Its value is primarily for the internist or to one who already has a fundamental knowledge of the subject. The details are not given which would be necessary for the book to be of value to the general practitioner. There are no vague statements; the author gets to his points quickly; and, as stated above, the book itself is very pleasant to read.

F. G. D.

Clinical Pathological Gynecology. By J. THORNWELL WITHERSPOON, B.S.; B.A. and M.A.; M.D. 400 pages; 24.5 × 15.5 cm. Lea and Febiger, Philadelphia. 1939. Price, \$6.50.

In the author's own words this book is ". . . a presentation of organic gynecological pathology and its clinical application. . . ." Intentional omissions by the author include discussions of embryology, congenital anomalies, clinical methods of examination and diagnosis, obstetrical injuries, malpositions of the uterus, and operative technic. The author has arranged the material under the headings of anatomical locations rather than under the similarity of diseases.

There are 13 sections and a total of 27 chapters. There are 271 illustrations which are clear and in the main are of gross and microscopic preparations. A few of the more important references are listed following each gynecological disease. There is an adequate index.

After describing the clinical pathologic features of each condition the author discusses treatment. Such an order provides the reader with a clear correlation of clinical, pathologic, and therapeutic factors rarely found in texts.

The sections on the anterior pituitary gonadotropic hormone and the ovarian hormones are sound, clear, informative, and bring up to date the knowledge regarding these hormones. Most controversial subjects are purposely merely touched upon, but the author definitely states his belief that the three common gynecological conditions of hyperplasia of the endometrium, uterine fibroids, and endometriomas have their origin in excessive stimulation of the various tissues concerned by the ovarian follicular hormone. Also there is a chapter on the relationship between estrogenic and carcinogenic principles.

There is an interesting chapter on the differential diagnosis of irregular uterine hemorrhage. Radium therapy is discussed in some detail.

Since the book presents such a refreshing approach to the correlation of clinical and pathologic gynecology, and since it is the result of the author's wide experience, it will be of value especially to the student and the practitioner.

J. E. S.

Biographies of Child Development. By ARNOLD GESELL, Ph.D., M.D., CATHERINE S. AMATRUDA, M.D., BURTON M. CASTNER, Ph.D., and HELEN THOMPSON, Ph.D. 328 pages; 24 × 16.25 cm. Paul B. Hoeber, Inc., New York City. 1939. Price, \$3.75.

Two sub-titles help describe this book. "The mental growth careers of eighty-four infants and children," and "A ten-year study from the Clinic of Child Development at Yale University."

In 1928 Dr. Gesell published *Infancy and Human Growth* in which he reported his mental-growth studies of 123 infants and discussed them from the standpoint of diagnosis and prognosis. Ten year follow-up studies are now reported on about 85 of these children.

These studies are discussed under a variety of headings. Cases are presented to illustrate normal, retarded and accelerated rates of mental growth. A great deal of valuable material is given to illustrate atypical growth complexes and the various factors that influence them. Thus cases are described to show the effect on mental growth of physical factors such as endocrine disturbances, birth injury and various infections involving the central nervous system. Other types of factors are also discussed, such as heredity, prematurity, reading disability and poor home environment. As sample illustrations of their findings, mental-growth studies of six children in one family show that heredity sometimes shows its effect in a bimodal distribution rather than a blend of two strains. Thus three of these children show normal mental-growth curves while three are definitely retarded. Another case illustrates an acceleration in mental-growth rate following removal from an orphanage and placement in a foster home.

The findings in this book are of particular interest to those professions dealing with children; pediatricians, educators, psychologists and social workers. The presentation is scientific in the strictest sense. There are no involved theories, nor does the reader have to wade through the strange jargons and terminologies characteristic of psychological schools of thought. The whole volume is readable, thought provoking and informative.

H. W. N.

The Medical Applications of the Short Wave Current. By WILLIAM BIERMAN, M.D. (Including a Discussion of Its Physical and Technical Aspects by MYRON M. SCHWARZSCHILD, M.A.). 379 pages; 23.5 × 16 cm. William Wood & Company, Baltimore. 1938. Price, \$5.00.

The author is one of this country's prominent specialists in Physical Therapy and a book by him on this important subject is quite welcome at this time. The subject deals with a comparatively recently developed physical modality that is apparently the most effective means of applying heat to the body, especially to its deeper portions. The nomenclature is still unsettled and it seems to this reviewer unfortunate that Dr. Bierman follows the German terminology in the use of the term "short wave" which is an inadequate designation. The distinction between long and short waves might apply to various portions of the electromagnetic range, to roentgen-rays, to actinic rays, to heat rays. Why should one assume that the term "short wave" refers only to the region of high frequency electrical phenomena? The term "diathermy" has been in common use for many years and "short wave diathermy," a designation widely used in this country, seems an adequate one. High frequency electrotherapy is another term that is sufficiently definite.

One of the useful features of the book is the discussion of the physical and technical aspects in which a physicist endeavors to present these factors to the reader with no great store of physics in his memory. He begins with the simpler electrical concepts and proceeds step by step to the complicated high frequency field. The uninitiated physician will find his ideas to some extent clarified by a single reading of

this section and doubtless much more so by re-reading it once or twice. To those interested in the physics of the radio it will, of course, be child's play for the application of this method to medicine has after all been a fortunate by-product of the intense activity of physicists in the field of radio communication.

Following the section on Physics, there are chapters on "Temperature Determination in the Living Human," "Physiologic Responses to Local Heat and Local Short Wave Currents," and "Specificity," after which in Part II, are considered "Technique" and "Clinical Applications." Each system of the body is taken up in turn. The sections on physiology and on clinical applications are really reviews of the world literature with the author's experience and opinions concerning those features with which he himself has worked. There is an imposing bibliography at the end of the volume and a good index.

One might wish that this well qualified author had given a more critical presentation of the clinical literature but he disclaims any such intention. He states, "We have attempted to indicate therapeutic evaluations based on our own clinical experiences as correctly as our limitations will permit. In the desire to make as wide reference as possible to the therapeutic experiences of others, we are noting them for the reader's information without attempting to evaluate their accuracy, and even though the assertions appear to us to be far-fetched."

T. P. S.

Behandlung rheumatischer Erkrankungen mit Ultra-Kurzwellen. By PROFESSOR DR. ERWIN SCHLIEPHAKE (Mit 27 Abbildungen). 105 pages; 22 × 14.5 cm. Theodore Steinkopff, Dresden and Leipzig. 1938.

Schliephake's name is more widely known than any other in the field of short wave diathermy. At about the same time the method was being developed in this country for the production of artificial fever, Schliephake in Germany, in 1929, was the first to use this electrical means for the treatment of local disease, and he has written voluminously concerning its use since that time. He is enthusiastic in regard to its possibilities and is an exponent of the idea that the electrical phenomena have some specific effect on the tissues and functions of the living body and are not effective merely by reason of the heat induced. Similarly he is inclined to attribute varying effects to different wave lengths.

There is little, however, concerning such theories in this small volume which is one of a series on "Rheumatism," edited by Professor Rudolf Jürgens. The author presents his views on the nature and etiological factors of rheumatic diseases and discusses the technic and results of treatment by means of ultra short wave diathermy. He makes use of wave lengths of 3 and 3½ meters, definitely shorter wave lengths (or higher frequency), than those available commercially in this country. Wave lengths below 6 meters are spoken of as ultra short waves.

Not only does this European author accept the doctrine of focal infections as a most important concept in the etiology and treatment of rheumatic diseases but he treats these foci of infection as well, with his ultra short waves. Furthermore he quotes and accepts Gutzeit and Küchlin's work to the effect that a treatment of a suspected dental granuloma by means of short wave diathermy will cause an increase in the sedimentation rate of the red blood cells if this granuloma is active as a focus of infection and hence gives valuable information as to whether or not this focus should be eradicated.

The author has had an extensive experience and the opinions expressed concerning his results in the treatment of infected foci and of the joints in different types of arthritis seem reasonably conservative. It is, however, a little disconcerting to have him state, as he does several times, that he not infrequently sees a favorable result of therapy appear as long as 6 or 8 weeks after the cessation of the treatment.

T. P. S.

COLLEGE NEWS NOTES

NEW LIFE MEMBER

Dr. C. D. Mercer, F.A.C.P., West Union, Iowa, became a Life Member of the American College of Physicians on July 29, 1939.

GIFTS TO THE COLLEGE LIBRARY

Grateful acknowledgment is made of the receipt of the following donations to the College Library of publications by members:

Reprints

- Dr. Benjamin M. Bernstein (Associate), Brooklyn, N. Y.—7 reprints;
Dr. Charles A. Bohnengel (Associate), New York, N. Y.—1 reprint;
Dr. William W. Cadbury, F.A.C.P., Canton, China—1 reprint;
Dr. H. M. Cleckley (Associate), Augusta, Ga.—1 reprint;
Dr. G. Philip Grabfield, F.A.C.P., Boston, Mass.—6 reprints;
Dr. Jacob Gutman, F.A.C.P., Brooklyn, N. Y.—7th, Second Series, Supplement to "Modern Drug Encyclopedia and Therapeutic Guide";
Dr. Ben R. Heninger, F.A.C.P., New Orleans, La.—5 reprints;
Dr. William G. Herrman, F.A.C.P., Asbury Park, N. J.—2 reprints;
Dr. L. Dale Huffman, F.A.C.P., Los Angeles, Calif.—1 reprint;
Dr. James H. Hutton, F.A.C.P., Chicago, Ill.—2 reprints;
Lt. Col. John G. Knauer, F.A.C.P., Denver, Colo.—1 reprint;
Dr. Sidney F. LeBauer (Associate), Greensboro, N. C.—1 reprint;
Dr. D. O. N. Lindberg, F.A.C.P., Decatur, Ill.—1 reprint;
Dr. Henry A. Monat (Associate), Washington, D. C.—3 reprints;
Dr. Samuel E. Munson, F.A.C.P., Springfield, Ill.—1 reprint;
Dr. Robert C. Page (Associate), Mount Vernon, N. Y.—4 reprints;
Dr. Albert E. Russell, F.A.C.P., Chicago, Ill.—1 reprint;
Dr. Paul F. Stookey, F.A.C.P., Kansas City, Mo.—1 reprint;
Dr. Herman Tarnower (Associate), Scarsdale, N. Y.—1 reprint;
Dr. Stuart L. Vaughan (Associate), Buffalo, N. Y.—1 reprint;
Dr. August A. Werner, F.A.C.P., St. Louis, Mo.—1 reprint.
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Dr. James G. Carr, F.A.C.P., College Governor for Northern Illinois, was elected President of the Chicago Society of Internal Medicine at its last annual meeting. Dr. LeRoy H. Sloan, F.A.C.P., was elected Vice-President.

Captain Frederick Ceres, F.A.C.P., has been appointed Medical Officer in command of the Medical Department of the U. S. Naval Air Station, Pensacola, Fla., this station being reputed to be the largest naval air station in the world.

Dr. J. C. Geiger, F.A.C.P., Director of Public Health of the City and County of San Francisco, on July 27, 1939 was awarded the honorary degree of Master of Arts in Medicine by the Hahnemann Medical College of Philadelphia, with the following citation:

"For his ability as a Health Officer as manifested by the outstanding merit credited to the Department of Public Health of San Francisco; for his research in public health problems, especially in the fields of food poisoning, epidemiology and communicable disease; for his inspiration and instruction as a teacher of the medical student and public health worker; for his high degree of integrity, tenacity of purpose and devotion to duty and public welfare, and the recognition of his personal characteristics of the true Southern Gentleman; for his love of home and family; for his contributions to science; and finally for his untiring and painstaking efforts in the practice of medicine in all its best aspects:—

"There is conferred upon Jacob Casson Geiger the honorary degree of Master of Arts in Medicine with all the rights and privileges appertaining thereto."

Dr. M. S. Rednick (Associate), Ossining, N. Y., addressed the Alumni of Lincoln Hospital, New York City, recently on "A Pathological Study of the Significance of the Systolic Murmur."

The Jefferson County (Alabama) Medical Society gave an informal subscription dinner, July 7, 1939, in Birmingham, for the presentation of citations for contributions to medicine beneficial to mankind, to Dr. Seale Harris, Sr., F.A.C.P., of Birmingham, and Dr. Tom D. Spies (Phillips Medallist of the A.C.P.), of Cincinnati. The Citation scroll was presented to Dr. Harris by Dr. M. S. Davie of Dothan, President of the Medical Association of the State of Alabama. The Citation scroll was presented to Dr. Spies by Dr. M. Y. Dabney, of Birmingham, Member of the State Board of Censors.

Dr. Solomon Solis-Cohen, F.A.C.P., Philadelphia, received the honorary degree of Doctor of Science (honoris causa) at the June, 1939, commencement of the Philadelphia College of Pharmacy and Science.

Dr. James Harvey Black, F.A.C.P., Dallas, has been elected president of the newly organized Texas Allergy Association.

Dr. Leslie M. Smith (Associate), El Paso, has been elected president of the Texas Dermatological Society for the current year.

Dr. Walter L. Treadway, F.A.C.P., formerly in charge of the U. S. Narcotic Farm at Lexington, Ky., has been assigned to the University of California Medical School, San Francisco, to direct a survey of the care of mental patients in the state.

Dr. Jacob J. Singer, F.A.C.P., Los Angeles, is director of the Rose Lampert Graff Foundation at the Cedars of Lebanon Hospital, Los Angeles, for the study of respiratory diseases. \$10,000 have been donated by Mr. and Mrs. Ellis Levy, Beverly Hills, for 1939, and plans are being considered to continue it for five years.

Dr. Charles H. Neilson, F.A.C.P., St. Louis, and Dr. E. Sanborn Smith, F.A.C.P., Kirksville, were recently appointed to the Missouri State Board of Health.

Dr. Eugene M. Landis, F.A.C.P., in 1936 Phillips Medallist of the American College of Physicians, assistant professor of medicine at the University of Pennsyl-

vania School of Medicine, has accepted the appointment as professor of internal medicine at the University of Virginia Department of Medicine, to succeed the late Dr. James C. Flippin.

Dr. Henry W. F. Woltman, F.A.C.P., Rochester, Minn., is a vice-president of the American Neurological Association for the current year.

Dr. Dudley W. Bennett, F.A.C.P., has been promoted to associate clinical professor of medicine at the University of California Medical School, San Francisco.

Dr. Edward J. Murray, F.A.C.P., Lexington, has been elected President of the Kentucky Hospital Association.

Dr. William Halsey Barker (Associate), instructor in medicine at Johns Hopkins University School of Medicine, Baltimore, has been appointed assistant dean. Dr. Barker will assist the dean in the field of student relations and will serve as a member of the committee on admissions to the medical school.

Dr. Guy W. Wells, F.A.C.P., Providence, is secretary of the Rhode Island Medical Society for the current year.

Dr. William H. Kelley (Associate) has been advanced to professor of medicine at the Medical College of the State of South Carolina, Charleston.

Dr. Hugh J. Morgan, F.A.C.P., professor of medicine at Vanderbilt University School of Medicine, Nashville, is one of those appointed recently by Governor Cooper to the "Advisory Board of Medical Care of State's Wards," to make a thorough study of the state's institutions and to recommend improvements in the present system of medical care for the inmates.

Major General Charles R. Reynolds, F.A.C.P., U. S. Army (Retired), has been elected president of the Association of Military Surgeons of the United States.

Dr. William E. Costolow, F.A.C.P., Los Angeles, is secretary of the American Radium Society.

Dr. Harold W. Gregg, F.A.C.P., Butte, has been installed as President of the Medical Association of Montana.

The advisory council on postgraduate medicine of the Wayne County Medical Society, Detroit, has determined upon an extension of its postgraduate program, and has elected officers including a secretary, executive secretary, and Dr. William J. Stapleton, Jr., F.A.C.P., as registrar. "The continuation school of medicine of Wayne County" will offer courses in the specialties to general practitioners, utilizing facilities of the county medical society, Wayne University College of Medicine, local hospitals, the Department of Welfare, and the Detroit Department of Health. It is proposed to start courses in the autumn with bedside teaching of general medicine, groups being limited to from four to six physicians. Other courses will be added as the program progresses.

The Seventh Annual Assembly of the Omaha Mid-West Clinical Society will be held at Omaha, October 23-27, 1939. Among distinguished guests presenting addresses and clinics are the following:

Medicine

Dr. Clifford J. Barborka, F.A.C.P., Chicago, Ill.

Dr. William R. Houston, F.A.C.P., Austin, Tex.

Dr. Samuel A. Levine, F.A.C.P., Boston, Mass.

RECENT ANNOUNCEMENTS

AMERICAN BOARD OF INTERNAL MEDICINE EXAMINATIONS

The next written examination by the American Board of Internal Medicine is scheduled for October 16, 1939, to be given in various centers. For specific information address the Secretary-Treasurer, Dr. William S. Middleton, 1301 University Ave., Madison, Wis.

ADVISORY COUNCIL ON MEDICAL EDUCATION

The Advisory Council on Medical Education has been organized with the following Officers and Executive Committee:

Officers

- Dr. Willard C. Rappleye, F.A.C.P., Dean of the Faculty of Medicine of Columbia University President
 Dr. Maurice H. Rees, Dean of the School of Medicine of the University of Colorado Vice-President
 Dr. Robin C. Buerki, Director of Study of the Commission on Graduate Medical Education Secretary-Treasurer

Executive Committee, Including the Above Officers and the Following:

- Dr. Anton J. Carlson, F.A.C.P., Professor of Physiology of the University of Chicago
 Dr. Harold Rypins, F.A.C.P., Secretary of the New York State Board of Medical Examiners
 Dr. Hugh J. Morgan, F.A.C.P., Professor of Medicine of Vanderbilt University
 Dr. Arthur W. Allen, Surgeon, Boston

The organizations represented on the Advisory Council are as follows:

- American College of Physicians—2 representatives;
 American College of Surgeons—2 representatives;
 Association of American Medical Colleges—3 representatives;
 American Hospital Association—3 representatives;
 Catholic Hospital Association—1 representative;
 Federation of State Medical Boards of the United States of America—3 representatives;
 Advisory Board for Medical Specialties—3 representatives;
 National Board of Medical Examiners—1 representative;
 Association of American Universities—2 representatives;
 American Public Health Association—1 representative;
 American Association for the Advancement of Science, Division of Medical Sciences—1 representative;
 American Protestant Hospital Association—1 representative;
 Association of American Colleges—2 representatives.

SUCCESSOR TO LATE DR. ALFRED STENGEL ANNOUNCED

Dr. Alfred Newton Richards, Professor of Pharmacology in the University of Pennsylvania School of Medicine, has been elected Vice-President of the University in charge of Medical Affairs to succeed the late Dr. Alfred Stengel. The selection of Dr. Richards, whose researches upon the mechanism of kidney function have won for him world wide acclaim, is a fortunate one for the University because he is in a position to strengthen and integrate research, teaching, and the practice of medicine. The successful performance of this function is vital to an institution where interest lies not only in the care of the sick, but also in a search for the cause and cure of disease. Through his own long experience in research both here and abroad Dr. Richards is eminently qualified for this task.

In recognition of his distinguished achievements in the field of medical research, Dr. Richards has been awarded the Kober Medal of the Association of American Physicians, the Gold Medal of the Academy of Medicine of New York, and the William Wood Gerhard Medal of the Philadelphia Pathological Society. In 1938 he was presented with the Philadelphia Award, which was endowed in 1921 by the late Edward W. Bok and is conferred annually in recognition of outstanding service to the community of which this city is a part. Dr. Richards has received honorary degrees from the University of Pennsylvania, Yale University, Western Reserve University, and the University of Edinburgh, Scotland.

ASSOCIATION OF MILITARY SURGEONS OF THE UNITED STATES

The Henry Wellcome Medal

The Wellcome Gold Medal and cash prize of \$500 awarded annually by the Association of Military Surgeons of the United States, was established in 1916 by the late Sir Henry Wellcome with the endorsement of the Council of the Association.

The Gold Medal, which was designed by Sir Henry Wellcome, bears on the reverse a representation of the seal of the Association of Military Surgeons of the United States. On the obverse are the heads of Machaon and Polaleirios, Homer's "two famed surgeons" of the Greek army in the Trojan War.

The Medal together with the cash prize is awarded annually "for researches, discoveries, inventions, designs, improvements, essays, or any other acts or deeds which the Executive Council of the Association may consider desirable and helpful to the objects of the Association, and relating to any phase of medico-military affairs and disease control associated with the Army, Navy, Militia and Public Health and Marine Hospital Service in times of peace or war at home or abroad."

Announcement of the annual competition is published each year in the official organ of the Association, "The Military Surgeon." The award is made for the best paper on the subject assigned each year in the published announcement. Additional particulars may be obtained by addressing the Secretary of the Association of Military Surgeons of the United States, Army Medical Museum, Washington, D. C. A replica of the Medal and an interesting history of its design have been presented to the American College of Physicians.

INSTITUTE FOR THE CONSIDERATION OF THE BLOOD AND BLOOD-FORMING
ORGANS

The University of Wisconsin Medical School will conduct an Institute for the Consideration of the Blood and Blood-Forming Organs, September 4-6, 1939, at Madison. The Wisconsin Alumni Research Foundation has made available the

necessary funds to finance this Institute. Among Fellows of the American College of Physicians who will participate on the program appear the following:

Dr. Charles A. Doan, Professor of Medicine at the Ohio State University, Leader of the Round Table on "The Etiology and Therapy of Granulocytopenia," an assistant to the leader in the Round Table on "Consideration of Some of the Diseases Affecting Lymph Nodes," and to deliver a paper on "The Reticulo-Endothelial System";

Dr. George R. Minot, Professor of Medicine and Director of the Thorndike Laboratory, Harvard Medical School, Leader of the Round Tables on "Etiologic and Therapeutic Aspects of the Hemorrhagic Diseases" and "Therapy of the Anemias," and to deliver a paper on "Anemias of Nutritional Deficiency";

Dr. Russell L. Haden, Chief of the Medical Division, Cleveland Clinic, to deliver a paper on "The Nature of the Hemolytic Anemias," and to act as a Leader of the Round Table on "Therapy of the Anemias";

Dr. Claude E. Forkner, Assistant Professor of Clinical Medicine, Cornell University Medical College, to deliver a paper on "Monocytic Leukemia and Aleukocythemmic Leukemia" and to assist the Leader in a Round Table on "The Treatment of Leukemia";

Dr. E. B. Krumbhaar, Professor of Pathology at the University of Pennsylvania School of Medicine, to deliver a paper on "Hodgkin's Disease" and to lead a Round Table on "Consideration of Some of the Diseases Affecting Lymph Nodes."

AMERICAN COLLEGE OF PHYSICIANS HOUSE COMMITTEE SOLICITS SUGGESTIONS

In the Board Room of the College Headquarters, 4200 Pine Street, Philadelphia, there is a wall space above the mantle, 43 inches broad and 36 inches high, which offers a splendid opportunity for an original painting or etching.

The Board Room is finished in oak paneling and the proposed painting will be the highlight of the room.

The House Committee desires suggestions from the membership at large in order that an appropriate and dignified work of art may be selected. One subject might represent some event in the development of medicine, preferably occurring in North America. Another possibility might be found in some historical event of importance in connection with the origin and growth of The College.

The House Committee will appreciate suggestions regarding the type and subject of the proposed picture. It will also be receptive to offers from any member who desires to underwrite same.

Communications should be addressed to the Chairman of the House Committee, Edward L. Bortz, M.D., 2021 W. Girard Avenue, Philadelphia, Pennsylvania.

OBITUARIES

DR. CHARLES ADDISON ELLIOTT

Charles Addison Elliott, Fellow of the American College of Physicians, died at the Passavant Memorial Hospital, Chicago, Illinois, on June 26, 1939, of cardiovascular disease.

Dr. Elliott was born in Lincoln, Nebraska, March 6, 1873. He received his degree of B.S. at the University of Nebraska in 1895 and in 1898 was graduated from Northwestern University Medical School. Following this, he served for a year and a half as an interne at the Mercy Hospital in Chicago. Later he studied at the University of Vienna and soon after began teaching at the Northwestern University Medical School. He continued in this department of Northwestern through the rest of his life, eventually attaining the position of Professor of Medicine, and for some twenty years serving as Chief of the Department of Medicine at the Northwestern University Medical School.

For many years, Dr. Elliott was a member of the staff of Wesley Memorial Hospital during a large part of which time he was the Chief of the Medical Staff. Since 1929 he was attending physician and Chief of the Medical Staff at the Passavant Memorial Hospital.

Dr. Elliott was a member of the Chicago Medical Society, the Illinois Medical Society and the American Medical Association. He served one year as Vice-President of the American Medical Association. He was a member of the Institute of Medicine of Chicago, which he also served as Vice-President for a term. He was a charter member of the Chicago Society of Internal Medicine, which he served as Secretary and as President. He was a member of the Association of American Physicians. He was active in the organization of the Central Society for Clinical Research. He was a member for many years of the Interurban Clinical Club of which he also served as Secretary and as President. He has been a Fellow of the American College of Physicians since 1929.

He published many articles in the current literature and was frequently called upon throughout the country for addresses on medical subjects.

Through many years Dr. Elliott has been regarded as one of the outstanding members of the medical profession in Chicago particularly in his chosen line of work—internal medicine. He had a wide practice as a consultant and was highly regarded by the profession. Practically from the time of his internship he was engaged in teaching. He was especially interested in his work at the Medical School and will be long remembered by hundreds of his students for his enthusiasm, his knowledge of medicine and his unusual capacity for teaching.

The profession in Chicago and throughout the country has lost a man of unusually attractive personality and character. Dr. Elliott will be especially mourned by those with whom he worked, his students, his associates in the Medical School, and the various societies of which he was a

member, by all those who were most closely associated with him. His interest in medicine and his skill in medicine combined with an unusual ability to teach were of service to students for many years. Yet, the greatest impression that Dr. Elliott made upon those who knew him was that of his own honesty, kindness, thoroughness and devotion to his patients; these things, he taught by example.

Dr. Elliott leaves a widow and three children. A son and daughter are both students in Northwestern University Medical School.

JAMES G. CARR, M.D., F.A.C.P.,
Governor for Northern Illinois.

DR. SAMUEL CALVIN SMITH

Dr. Samuel Calvin Smith of Philadelphia, a Fellow of the American College of Physicians since April 5, 1923, died July 31, 1939, in the General Hospital, East Stroudsburg, from injuries suffered in an automobile accident.

Dr. Smith was born in Hollidaysburg, Pennsylvania, February 28, 1881, and was educated there and at Bucknell University, from which he was graduated in 1901. After receiving his medical degree from Jefferson Medical College of Philadelphia, he returned to his native city to practice until 1916.

During the World War, Dr. Smith served as a major in the Army Medical Corps in France. He later became Instructor in medicine at Jefferson, which position he held from 1920 to 1922, and remained in Philadelphia to practice. He was consulting cardiologist from 1925 to 1930 at the Misericordia Hospital and West Chester Hospital and during 1931-32 at the Veterans' Hospital, Coatesville.

In addition to being a Fellow of the American College of Physicians, Dr. Smith belonged to the American Medical Association, and was a member of its special committee for the presentation of modern methods of heart study.

The passing of Dr. Smith leaves a large circle of friends who will greatly miss this eminent physician.

EDWARD L. BORTZ, M.D., F.A.C.P.,
Governor for Eastern Pennsylvania.

DR. PHILIPS J. EDSON

Dr. Philips J. Edson, F.A.C.P., died on July 6, 1939, from coronary sclerosis, at his home in San Marino, California. Dr. Edson was born November 27, 1896, at Los Angeles. He attended the Manual Arts High School, received his A.B. degree in 1920, his M.A. degree in 1921 and his M.D. degree in 1924 from the University of California. He was an Assistant in Physiology at the University of California while working for

his M.A. degree; he interned at the Peter Bent Brigham Hospital in Boston from 1923 to 1925, and began practice in Pasadena in 1926; for a number of years he was Instructor in Medicine at the College of Medical Evangelists, Physician to the Los Angeles County Hospital and Senior Visiting Physician and Vice Chairman of the Medical Staff to the Huntington Memorial Hospital of Pasadena. He was particularly interested in internal Medicine and Cardiology.

Dr. Edson was a member of the Los Angeles County Medical Association, California State Medical Association, Los Angeles Clinical and Pathological Society, American Medical Association, California Heart Association, and had been a Fellow of the American College of Physicians since 1938. He was a member of Pasadena's University and Valley Hunt Clubs and the Rotary Club, and was well known and well liked by both his conferees and a wide circle of friends and acquaintances. He was a good physician who will be much missed by his friends and a sorrowing family.

EGERTON L. CRISPIN, F.A.C.P.,
Regent.

DR. MARY PRIESTLEY SHERIFF RUPERT

Dr. Mary Priestley Sheriff Rupert, F.A.C.P., of Bala-Cynwyd, Pennsylvania, a Fellow of The American College of Physicians since 1928, died July 21, 1939.

Dr. Rupert was born in Shamokin in 1880. She was graduated from the Woman's Medical College of Pennsylvania in 1904, and then interned at its hospital.

Dr. Rupert received postgraduate training at the University of Edinburgh, Scotland, Johns Hopkins University School of Medicine, Harvard University Medical School and the New York Polyclinic Medical School.

Dr. Rupert was responsible for organizing the laboratory of clinical pathology at the Woman's Medical College where she was Clinical Professor of Medicine. For the last two years she had served on the executive committee of the Board of Corporators. She was on the board as representative of the alumnae of the college. In recent years she retired from the active practice of medicine.

Dr. Rupert was a member of the American Medical Association, Philadelphia County Medical Society, Pennsylvania State Medical Society, The American College of Physicians, and the American Medical Women's Association.

Dr. Rupert leaves a large circle of friends and professional colleagues with whom she has been on the most intimate terms and by whom she will be greatly missed.

EDWARD L. BORTZ, M.D., F.A.C. P.,
Governor for Eastern Pennsylvania.

DR. CARROLL JULIAN ROBERTS

With the death of Dr. Carroll Julian Roberts on April 6, 1939, Buffalo lost one of its outstanding citizens and the medical profession a distinguished member.

Dr. Roberts was born in Buffalo, New York, June 9, 1880, and was graduated from the University of Buffalo School of Medicine in 1903. He continued study in Berlin—at the Friedrichain Krankenhaus and the Charité Krankenhaus.

In 1934 Dr. Roberts was in charge of medical teaching at the Buffalo City Hospital with the rank of Professor of Medicine; Assistant Attending Physician at the Buffalo General Hospital; Director of the Peripheral Vascular Clinic at the Buffalo General Hospital and Consulting Physician at the J. N. Adam Memorial Hospital at Perrysburg.

He was a member of the Academy of Medicine, Erie County Medical Society, Medical Union, American Medical Association and a Fellow of the American College of Physicians since 1931. He served as Chairman of the Health Board, which post he resigned to accept the position of Clinical Director of the Buffalo City Hospital.

Dr. Roberts was a consistent, conscientious student and a splendid teacher. He had a wonderful personality and, in every way, showed himself to be a high type of medical teacher and practitioner.

NELSON G. RUSSELL, SR., M.D., F.A.C.P.,
Governor for Western New York.

ANNALS OF INTERNAL MEDICINE

VOLUME 13

SEPTEMBER, 1939

NUMBER 3

THE SIGNIFICANCE OF POST-PRANDIAL GLYCO- SURIA IN THE TREATMENT OF DIABETES MELLITUS WITH PROTAMINE ZINC INSULIN *

By I. M. RABINOWITCH, F.A.C.P., *Montreal, Canada*

PROTAMINE zinc insulin is now a definitely established therapeutic agent for the treatment of diabetes mellitus. Judging from the literature, most of the difficulties which were met with, following our first reports ^{1, 2, 3} of the product now in general use † appear to have been overcome. Theoretically, protamine zinc insulin appeared to be contraindicated in conditions for which quick action is necessary, though this also was contrary to our experiences. Coma is an example. Because of its slow action in ordinary amounts, it was repeatedly stated in the literature that protamine zinc insulin is contraindicated in coma. Actually, as we have shown ⁴ it is not only not contraindicated, but is ideal, when employed under the conditions described.

POST-PRANDIAL GLYCOSURIA

A condition which is not infrequently met with in the use of protamine zinc insulin is *post-prandial* glycosuria; the sugar appears in the urine after meals, but disappears thereafter, so that the following morning the urine is not only free of sugar but the blood sugar is perfectly normal. The excretion of the sugar is preceded by an increase of the sugar in the blood. The duration of the hyperglycemia is, however, variable; the blood sugar may remain high for some hours or return to the normal or nearly normal level within an hour or less. Protamine zinc insulin thus resembles unmodified insulin and the phenomenon is not unlike that observed occa-

* Received for publication August 16, 1938.

From the Department of Metabolism, The Montreal General Hospital, Montreal, Canada.

† Though attempts had been made by other workers to prolong the action of insulin and of Hagedorn's protamine insulin, the product upon which these reports were based was that first prepared by Scott and Fisher in the Connaught Laboratories, of the University of Toronto, and supplied to this hospital for clinical trial. It is the protamine zinc insulin which is now in general use.

sionally after ingestion of glucose without insulin.⁵ Frank⁶ first observed that once sugar appears in the urine it may continue to do so for some time, though the blood sugar has decreased below the generally accepted level of the renal threshold for glucose or has actually reached the normal level.

POST-PRANDIAL GLYCOSURIA AND CARBOHYDRATE TOLERANCE

Ordinarily, when the carbohydrate content of the diet of the diabetic is gradually increased, the appearance of sugar in the urine indicates the limit of carbohydrate tolerance; carbohydrates added to the diet thereafter are excreted practically quantitatively—Allen's Paradoxical Law. A careful investigation of our cases, however, has shown that, in spite of the appearance of sugar in the urine, the carbohydrate content of the diet could be increased without a corresponding increase of glycosuria. An example is shown in table 1. It will be noted that when the total available glucose

TABLE I
Showing Relationship between Intake and Excretion of Sugar during Treatment with
Protamine Zinc Insulin
(Hosp. No. 2706/37)

Date	Diet (Grams)				Urine			Blood Sugar (%)	Body Weight (lbs.)	Pro- tamine Zinc Insulin		
	COH	Fat	Prot.	Total G*	Vol.	Sugar						
						%	Gm.					
Aug. 24/37.....	250	45	100	310	2950	+		0.285	160	30-0-0		
Aug. 25.....					+		0.107					
Aug. 26.....					2450	2.0	49	0.116			157	
Aug. 27.....					1925	1.0	20	0.107			156	
Aug. 28.....					2050	1.5	31	0.103			158	
Aug. 29.....	300	45	100	360	1925	tr.						
Aug. 30.....					2100	2.3	49	0.100	157			
Aug. 31.....					1950	1.9	37	0.100	158			
Sept. 1.....					2750	2.0	55	0.135	156 $\frac{1}{2}$			
Sept. 2.....					1875	2.2	41	0.100	157 $\frac{1}{4}$			

$$* G = C + 0.1 F + 0.58 P$$

of the diet was increased from 310 to 360 grams per day—that is, 50 grams—the average daily excretion of sugar in the urine had increased from 37.2 to 44.3 grams—that is, about 6 grams only—and with one exception only, the blood sugar was still perfectly normal in the fasting state.

Clinically, judging from appearance in general, body weight, activity, etc., the impression has been that this post-prandial glycosuria is not harmful. The findings in general fit in with the observation by Mosenthal⁷ that small amounts of sugar may be eliminated in the urine without detrimental results—that glycosuria is harmful only when it is accompanied by polyuria with its resultant dehydration. They also fit in with the observation by Wilder and Wilbur⁸ that, even in the difficult cases with the use of prota-

mine zinc insulin, where in spite of intermittent glycosuria which it was necessary to maintain in order to avoid hypoglycemic reactions, the patients seemed to feel healthier and stronger than they had before. They also fit in with an idea which is receiving increasing support, namely, that hyperglycemia is not always harmful. In fact, judging from experiences with diabetics with cardio-vascular disease^{7, 9} and experiments in animals¹⁰ it would appear that an increase of sugar in the blood may be beneficial at times—that, within certain limits, it may actually aid the utilization of carbohydrates. In the past, however, judging from our experiences with the metabolism of cholesterol, when our diabetics were treated with high fat diets, hyperglycemia and glycosuria, even when transient, appeared to be harmful.^{11, 12, 13} It was, therefore, considered necessary to investigate the cholesterol metabolism in these cases of post-prandial glycosuria following treatment with protamine zinc insulin.

BASIS OF USE OF CHOLESTEROL AS AN INDEX OF PROGRESS

The cholesterol content of the blood may fluctuate widely in diabetes, not only in different individuals but in the same person at different times. Statistically, however, in the past it was found to be the most reliable index of progress. Joslin and his associates^{14, 15, 16, 17} who have had a similarly large experience, and who first suggested this test, still agree with this view.¹⁸ According to McEachern and Gilmour¹⁹ consecutive daily estimations in the same patient give widely varying results, and prove the fallacy of studying the blood cholesterol except under most rigidly controlled conditions. This view, however, was based upon 140 tests in 28 normal subjects; whereas the experiences with diabetics included many thousands of tests during periods of many years. The experiences at The Montreal General Hospital alone include over 15,000 tests on diabetics. The reliability of the test as an index of progress is shown in table 2 in which

TABLE II
Showing Relationship between Degree of Control of Diabetes and
Cholesterol Content of Blood Plasma

Frequency of Glycosuria	Average Plasma Cholesterol (per cent)	
	Adults *	Children †
Urine sugar free: blood sugar normal.....	0.184	0.176
Urine sugar free: blood less than 0.18%.....	0.209	0.224
Glycosuria once a month.....	0.230	0.220
Glycosuria twice a month.....	0.252	0.286
Glycosuria once a week.....	0.272	0.260
Glycosuria twice a week.....	0.288	0.264
Glycosuria daily, but free at times.....	0.320	0.236
Glycosuria persistent.....	0.379	0.350

* RABINOWITCH, I. M.: Arch. Int. Med., 1929, xliii, 363.

† RABINOWITCH, I. M.: Arch. Int. Med., 1929, xliii, 372.

are briefly summarized tables 1 and 2 of a previous report of adults¹² and tables 1 and 2 of a similar report of juvenile diabetics.¹³ This study included over 2000 observations in 431 diabetics. The data show the relationship found between the frequency of glycosuria and the cholesterol content of the blood plasma. It will be noted that the cholesterol content of the blood plasma increased as the glycosuria became more frequent. That the differences noted between the average cholesterol values were significant was shown by the ratios of the differences to their "probable errors." For purposes of brevity, the reader is referred to the original papers for the mathematical proof.

RELIABILITY OF PLASMA CHOLESTEROL WITH HIGH CARBOHYDRATE-LOW CALORIE DIET

The above experiences, it should be noted, were prior to 1930 and, therefore, at the time when our diets contained large amounts of fat. Since

TABLE III
Showing Relationship between Control Index and Cholesterol Content of
Blood Plasma in Uncomplicated Diabetes
(1037 Observations in 187 Diabetics)

Group	Control Index (Range)	Number of Cases	Plasma Cholesterol					
			M	σ	PEm	Δ	PE Δ	$\frac{\Delta}{PE\Delta}$
1	-1.00	23	277	58	8.10	24	9.8	2.4
2	1.01-1.50	27	253	43	5.54	25	6.6	3.8
3	1.51-2.00	40	228	34	3.60	18	4.9	3.7
4	2.01-2.50	45	210	34	3.30	29	5.8	5.0
5	2.51-3.00	52	181	51	4.73			

Milligrams per 100 c.c. plasma.

M —Mean

σ —Standard deviation.

PEm—Probable error of mean.

Δ —Difference between means.

PE Δ —Probable error of differences.

From: RABINOWITCH, I. M.: ANN. INT. MED., 1935, viii, 1436.

then we have used the high carbohydrate-low calorie diet²¹ practically exclusively* and one of the characteristics of this diet, as was shown, is an immediate and sustained reduction of the plasma cholesterol. Therefore, before the cholesterol content of the blood plasma may be used to test the

* A number of changes have been made since our first report of this diet in 1930, in order to make it more attractive—increase of meat or fish, frequent feedings, etc.—but there have been no radical changes; the average diet still consists of, approximately, 260 grams of carbohydrate, 45 grams of fat and 100 grams of protein.

significance of the post-prandial glycosuria noted with protamine zinc insulin, it must be determined definitely whether plasma cholesterol is still a reliable index of progress. That it is, was clearly shown in a study by the writer²² of 1037 observations in 187 diabetics who had no complications which are known to either increase or decrease the cholesterol content of the blood plasma, independent of the degree of control of the diabetes. A summary of these experiences is shown in table 3 which is a reproduction of part of the previously published table. In this investigation, the cholesterol content of the blood plasma was compared with the degree of control of the diabetes and the latter was judged by the Control Index.[†]

RELIABILITY OF PLASMA CHOLESTEROL WITH PROTAMINE ZINC INSULIN

A possibility which had to be considered was that protamine zinc insulin may, per se, influence the metabolism of cholesterol and thus limit the value of the test as an index of progress. That protamine zinc insulin has not altered the reliability of this test is shown in tables 4 and 5.

TABLE IV

Showing Relationship between Control Index and Cholesterol Content of Blood Plasma in Diabetics Treated with Protamine Zinc Insulin
(1000 Observations in 161 Cases)

Group	Control Index (Range)	Number of Cases	Plasma Cholesterol					
			M	σ	PEm	Δ	PE Δ	$\frac{\Delta}{PE\Delta}$
1	-1.00	0						
2	1.01-1.50	8	247	38	9.00	35	10.0	3.5
3	1.51-2.00	19	212	26	4.51	30	7.3	4.1
4	2.01-2.50	41	182	41	5.85	9	9.0	1.5
5	2.51-3.00	93	173	32	2.00			

Milligrams per 100 c.c. plasma.

M —Mean

σ —Standard deviation.

PEm—Probable error of mean.

Δ —Difference between means.

PE Δ —Probable error of differences.

Table 4 shows the relationship found between the Control Index and the cholesterol content of the blood plasma. The data clearly indicate that protamine zinc insulin has not altered the reliability of the cholesterol content of the blood plasma as an index of progress, though the average values are lower than those shown in table 3 with similar disturbances of the diabetes.

[†] The Control Index is used in this Clinic as a quantitative guide of the degree of control of the diabetes. The details of this Index were dealt with in a previous communication.²²

TABLE V

Showing Relationship between Cholesterol Content of Blood Plasma and Insulin Dosage after One Year of Treatment with Protamine Zinc Insulin

Group	Control Index		Number of Cases	Average Chol. %	Insulin Dosage					
					Increased		Stationary		Decreased	
	Range	Average			No.	%	No.	%	No.	%
1	1.01-1.50	1.35	8	0.247	6	75.0	2	25.0	0	0
2	1.51-2.00	1.86	19	0.212	11	57.9	7	36.8	1	5.3
3	2.01-2.50	2.21	41	0.182	8	19.5	26	63.4	7	17.0
4	2.51+	2.63	93	0.173	5	5.4	31	33.3	57	61.3

Table 5 is a confirmation of the results shown in table 4. It shows the relationship found between the cholesterol content of the blood plasma and insulin dosage in the same cases. The data include 161 diabetics treated with our high carbohydrate-low calorie diet and with protamine zinc insulin for an average period of one year. It will be noted that of the 93 patients whose average plasma cholesterol was perfectly normal, namely, 0.173 per cent, 57—an incidence of 61.3 per cent—were able to reduce their insulin dosage; whereas, of the 41 whose average plasma cholesterol was just at the upper level of normality, namely, 0.182 per cent, 7 only—that is, 17 per cent—were able to reduce their dosage, and of the 9 whose average plasma cholesterol was definitely above the normal, one only was able to reduce the insulin dosage.

POST-PRANDIAL GLYCOSURIA AND PLASMA CHOLESTEROL

Having found that the cholesterol content of the blood plasma is a reliable index of progress with the combined use of the high carbohydrate-low calorie diet and protamine zinc insulin, it is now possible to determine the effects of the post-prandial glycosuria with a reasonable degree of accuracy. For this purpose, the last 1500 plasma cholesterol determinations were correlated with the blood and urinary sugar findings. A summary of the data is shown in table 6.

TABLE VI

Showing Relationship between Hyperglycemia and Cholesterol and Absence of Relationship between Transient Glycosuria and Cholesterol

	Blood sugar normal			Blood sugar increased		
	All Values	No Glycosuria	Transient Glycosuria	All Values	0.121 to 0.180	0.181+
Number.....	811	507	304	689	427	262
Average Cholesterol (mg. per 100 c.c.).....	176	174	179	191	186	199

It will be noted that the 1500 observations are divided into two groups, namely (a) those with normal blood sugars and (b) those in which the sugar content of the blood was increased. The data, thus divided, show that the average cholesterol content of the blood plasma in the group with normal blood sugars was 0.176 per cent; whereas in the group in which the blood sugars were increased it was 0.191 per cent. The difference is not very great. That the plasma cholesterol reflects the degree of control of the diabetes, is more definitely shown by dividing all of the data of the second group into two other groups, namely: (a) Those in which the bloods were moderately hyperglycemic only (blood sugar range = 0.121 to 0.180 per cent); and (b) those in which the bloods were markedly hyperglycemic (blood sugar = 0.181 per cent or more). With this division, it will be

TABLE VII

Showing Statistical Proof of the Harmlessness of Post-Prandial Glycosuria in Diabetics Treated with the High Carbohydrate-Low Calorie Diet and Protamine Zinc Insulin

	Blood sugar normal		Blood sugar increased	
	No Glycosuria	Glycosuria	0.121 to 0.180	0.181+
Number of tests.....	507	304	427	262
Average plasma cholesterol *.....	174	179	186	199
σ	47	61	53	67
PEm.....	1.40	2.35	1.72	2.78
Δ	5	7	13	
PE Δ	2.73	2.91	3.34	
Δ				
PE Δ	2.8	2.4	3.9	

σ = Standard deviation.

PEm = Probable error of mean.

PE Δ = Probable error of difference.

Δ = Difference between means.

* mg. per 100 c.c.

noted that whereas with the normal blood sugars, the average cholesterol value was 0.176 per cent with the moderate hyperglycemia, it was 0.186 per cent and with marked hyperglycemia it was 0.199 per cent.

In view of the above findings, the *normal* blood sugar values were divided into groups, namely, (a) those with and (b) those without post-prandial glycosuria. It will be noted, however, that with this division, the average cholesterol content of the blood plasma was practically the same, namely, 0.174 and 0.179 per cent respectively.

The significances of the differences between the different averages were judged by their "probable errors." The results are shown in table 7. Briefly, they indicate that, whereas there were significant differences between the cholesterol values of those with and those without an increase of blood

sugar and between those with moderate, and those with marked, hyperglycemia, the difference between the average of those with and those without post-prandial glycosuria, but with normal blood sugars, was not significant. The conclusion, therefore, is that the post-prandial glycosuria in diabetes treated with protamine zinc insulin, when associated with a perfectly normal blood sugar in the fasting state, is not harmful. This conclusion, it should be pointed out here, is based entirely upon use of protamine zinc insulin with our high carbohydrate-low calorie diet. It may or may not apply to other diets.

Since this paper was submitted for publication, a similar analysis was made of another 1500 cholesterol determinations and the results were essentially the same. The data fit in with the lesser importance which is now being attached to glycosuria in the diabetic than in the past. Himsworth,²³ for example, now restricts the "post-absorptive glycosuria within reasonable limits" and Priscilla White²⁴ no more insists upon sugar-free urine in the treatment of juvenile diabetics. In fact, Dr. White now²⁵ regards the diabetes under good control though as much as 10 to 20 per cent of the total carbohydrate of the diet may be excreted in the urine. This, according to some of the diets used by Dr. White, amounts to 20 to 40 grams of sugar. The explanation of the discrepancy between past and present practices is, I believe, to be found in the change of the diet of the diabetic—more liberal use of carbohydrate and reduction of fat. An analogy is found in the experiences with protein. With the old low carbohydrate-high fat diets large quantities of protein were avoided because they were known to have been harmful; whereas, with our high carbohydrate-low calorie diet, we have not only found liberal amounts of protein not harmful but, actually, beneficial; they promote skeletal growth in the child and improve health in general in the adult. Very few of our adult diabetics now receive less than 100 grams of protein a day. The ability to tolerate liberal amounts of protein is due to the increase of carbohydrate and reduction of fat in the diets; the diets no longer approximate the exclusively fat-protein diet which was known to convert a mild into a severe diabetes in man and to cause complete diabetes in the partially depancreatized animal.

This work was done with the aid of a Grant from Mr. J. C. Newman, President, and Mr. Julian C. Smith, member of the Board of Management, of The Montreal General Hospital.

REFERENCES

1. RABINOWITCH, I. M., FOSTER, J. S., FOWLER, A. F., and CORCORAN, A. C.: Clinical experiences with protamine zinc insulin and other mixtures of zinc and insulin in diabetes mellitus, *Canad. Med. Assoc. Jr.*, 1936, xxxv, 239.
2. RABINOWITCH, I. M., FOWLER, A. F., and CORCORAN, A. C.: Further observations on the use of protamine zinc insulin in diabetes mellitus, *Canad. Med. Assoc. Jr.*, 1937, xxxv, 111.
3. FOWLER, A. F., BENSLEY, E. H., and RABINOWITCH, I. M.: Control of diabetes mellitus with protamine zinc insulin in surgery, *Canad. Med. Assoc. Jr.*, 1937, xxxvi, 561.
4. RABINOWITCH, I. M., FOWLER, A. F., and BENSLEY, E. H.: The use of protamine zinc insulin in diabetic coma, *Canad. Med. Assoc. Jr.*, 1937, xxxvii, 105.
5. RABINOWITCH, I. M.: The diagnosis of diabetes, *Trans. Assoc. Life Ins. Med. Dir. N.A.*, 1933, xx, 9.
6. FRANK, E.: Über experimentelle und klinische Glykosurien renalen Ursprungs, *Arch. f. exper. Path. u. Pharmacol.*, 1913, lxxii, 387.

7. MOSENTHAL, H. O.: Hyperglycaemia, *Jr. Am. Med. Assoc.*, 1935, cv, 484.
8. WILDER, R. M., and WILBUR, D. L.: Diseases of metabolism and nutrition, *Arch. Int. Med.*, 1937, lix, 329.
9. SOSKIN, S., KATZ, L. N., STROUSE, S., and RUBINFELD, S. H.: Treatment of elderly diabetic patients with cardiovascular disease, *Arch. Int. Med.*, 1933, li, 122.
10. WIERZUCHOWSKI, M.: Oxidation of glucosc as function of its supply, *Jr. Physiol.*, 1937, xc, 440.
11. RABINOWITCH, I. M.: The cholesterol content of the blood plasma as an index of progress in insulin-treated diabetics, *Canad. Med. Assoc. Jr.*, 1927, xvii, 171.
12. RABINOWITCH, I. M.: The cholesterol content of blood plasma in diabetes mellitus, *Arch. Int. Med.*, 1929, xliii, 363.
13. RABINOWITCH, I. M.: The cholesterol content of blood plasma in juvenile diabetics, *Arch. Int. Med.*, 1929, xliii, 372.
14. GRAY, H.: Lipoids in 1000 diabetic bloods, *Am. Jr. Med. Sci.*, 1924, clxviii, 35.
15. HUNT, H. M.: Cholesterol in blood of diabetics treated at New England Deaconess Hospital, *New England Jr. Med.*, 1929, cci, 659.
16. WHITE, P., and HUNT, H.: Cholesterol of blood of diabetic children, *New England Jr. Med.*, 1930, ccii, 607.
17. JOSLIN, E. P.: Fat and the diabetic, *New England Jr. Med.*, 1933, ccix, 519.
18. JOSLIN, E. P.: Treatment of diabetes mellitus, 6th Ed., 1937, Lea and Febiger.
19. McEACHERN, J. M., and GILMOUR, C. R.: Studies in cholesterol metabolism, *Canad. Med. Assoc. Jr.*, 1932, xxvi, 30.
20. RABINOWITCH, I. M.: Diabetic gangrene, *Canad. Med. Assoc. Jr.*, 1927, xvii, 27.
21. RABINOWITCH, I. M.: Experiences with high carbohydrate-low calorie diet for treatment of diabetes mellitus, *Canad. Med. Assoc. Jr.*, 1930, xxiii, 489; *New England Jr. Med.*, 1931, cciv, 799; *Canad. Med. Assoc. Jr.*, 1932, xxvi, 141.
22. RABINOWITCH, I. M.: Arteriosclerosis in diabetes, *ANN. INT. MED.*, 1935, viii, 1436.
23. HIMSWORTH, H. P.: Protamine insulin and protamine zinc insulin in the treatment of diabetes mellitus, *Brit. Med. Jr.*, 1937, i, 541.
24. WHITE, PRISCILLA: Protamine insulin in the treatment of juvenile diabetes, *South. Med. Jr.*, 1938, xxxi, 15.
25. WHITE, PRISCILLA: Treatment of diabetic girls, *Jr. Am. Med. Assoc.*, 1939, cxii, 1440.

A FAMILY OUTBREAK OF TYPE V PNEUMOCOCCUS INFECTIONS: CLINICAL, BACTERIOLOGICAL AND IMMUNOLOGICAL STUDIES *

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TILGHMAN and Finland² recently reported 33 groups of multiple contact cases of pneumococcal infections, including five family groups, in which bacteriological and immunological studies were made.³ The present paper concerns similar observations in another family consisting of 11 members, 9 of whom had infections with type V (Cooper¹) pneumococci and a tenth member carried the same organism while apparently remaining free of symptoms. Early in the course of this investigation, type VI pneumococci were cultured from the throat of one individual in the same family and pneumococci of this type were subsequently isolated from the throats of six of the 11 members, none of whom had infections attributable to this organism. During the fourth week of this study, beta hemolytic streptococci were cultured from the throats of seven members of the family, including two with tonsillitis and one with a sore throat.

MATERIALS AND METHODS

The course of the outbreak and the factors determining its spread were studied by observation of the three members of the family who were admitted to the hospital and by periodic visits to the home. The epidemiologic data were obtained with the assistance of Dr. C. D. Cunningham, epidemiologist for the State of Connecticut, while he was attending the Harvard School of Public Health. Cultures were made of sputum, pharyngeal swabs and aural discharges, and blood samples for serological studies were obtained from the various members of the family. The bacteriological studies were concerned mainly with the isolation and identification of pneumococci and their types. The immunological studies consisted of tests for agglutinins and for mouse protective antibodies in the serum. The methods employed and the organisms used for the serological tests were similar to those used in previous studies.^{2, 3}

CLINICAL, BACTERIOLOGICAL AND IMMUNOLOGICAL OBSERVATIONS

The occurrence of respiratory tract infections (including middle ear infections) and the results of the bacteriological studies are represented graphically in figure 1. These data and the results of the immunological tests are listed in table 1. The findings may be summarized briefly.

* Received for publication May 28, 1938.

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This investigation was aided, in part, by a grant given in honor of Francis Weld Peabody by the Ella Sachs Plotz Foundation.

This work was carried out with the technical assistance of Mrs. Mildred W. Barnes.

Three children of family H. were admitted to the Boston City Hospital on April 27, 1937. Each of these three children was found to have lobar pneumonia involving the right lower lobe; each had or soon developed bilateral suppurative otitis media; and type V pneumococci were isolated from the purulent aural discharge and from the sputum or throat culture in each case. While the children were in the hospital, and again after they were discharged, visits were made to the home of this family. Careful inquiries

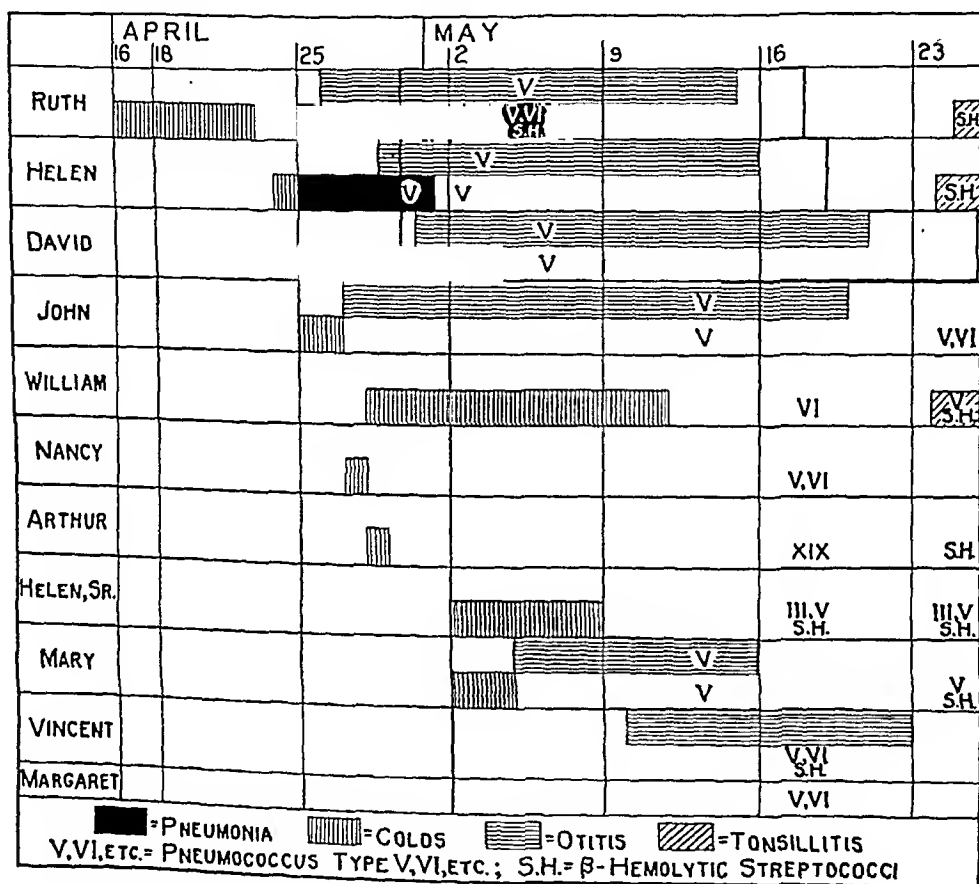


FIG. 1. Spread of respiratory infections in family H. The heavier lines enclose the interval of hospitalization.

were made concerning respiratory tract infections in all the members of the family, cultures were made of the throats and of any aural discharge observed, and blood was taken to determine whether specific antibodies had developed against any of the types of pneumococci encountered.

No other cases of pneumonia developed in the family, but three other siblings became ill with otitis media and, in each instance, type V pneumococci were obtained on culture from the aural discharge or from the throat or from both. Pneumococci of this type were also isolated on one or more occasions from the throats of both parents and from two other siblings. One of the latter (Nancy) was apparently free of infections

TABLE I
Clinical, Bacteriological and Immunological Data

Name	Age yrs.	Clinical	Bacteriology			Immunology			
			Date	Throat	Ear	Date	Agglu- tinins†		Protec- tion
							V	VI	
Ruth	7	Apr. 16: Coryza, cough 1 week Apr. 25: L. pneum.; crisis May 7 Apr. 26: Bilat. O. M. A.; draining Apr. 27 to May 15 Apr. 29: Adm. B. C. H.; disch. May 18 May 25: Tonsillitis	May 6 May 25	V, VI, S. H. S. H.	V	May 6	1:8	0	1,000,000
Helen	15	Apr. 24: slight cough Apr. 25: L. pneum.; serum Apr. 30: crisis May 1 Apr. 29: Adm. B. C. H.; disch. May 19 Apr. 30: Bilat. O. M. A.; draining May 3 to May 16 May 24: Tonsillitis	Apr. 29 May 2 May 25	V* V* S. H.	V	Apr. 30† May 1† May 11	0 1:32 1:2	0 0 1:4	0 10,000,000 1,000,000
David	2½	Apr. 25: L. pneum.; crisis May 4 Apr. 29: Adm. B. C. H.; disch. May 25 Apr. 30: Bilat. O. M. A.; draining to May 21	May 6	V	V	May 6	1:2	0	10,000
John	9	Apr. 25: "Cold," fever, in bed to May 9 Apr. 27: Bilat. O. M. A.; draining to May 22	May 13 May 25	V V, VI	V	May 19	1:2	0	100,000
William	43	Apr. 28: "Cold," cough—2 weeks May 24: sore throat	May 19 May 25	VI V, S. H.		May 19	1:2	0	100,000
Nancy	4	Apr. 28: "Cold," cough, fever—1 day	May 19	V, VI		May 19	0	0	10,000
Arthur	1½	Apr. 29: Fever, malaise—1 day	May 19 May 25	XIX S. H.		—	—	—	—
Helen, Sr.	43	May 2: Cough, fever, headache—1 week	May 19 May 25	III, V, S. H. III, V, S. H.		May 19	1:4	0	1,000,000
Mary	18	May 2: Coryza May 6: Left O. M. A.; draining May 7 to May 15	May 13 May 25	V V, S. H.	V	May 19	1:2	0	100,000
Vincent	17	May 10: Bilat. O. M. A.; no drainage, well May 22	May 19	V, VI, S. H.		May 19	0	0	100,000
Margt.	12	No illness	May 19	V, VI		May 19	0	0	100,000

Explanation:

* Sputum culture.

† Blood cultures at this time showed no growth.

‡ All sera were tested for type III and type XIX agglutinins and found negative.

Agglutinins: 1:2, 1:4, etc. = greatest dilution showing floccular agglutination.

Protection: mouse protective antibodies in lethal doses per 0.2 c.c. of serum.

Abbreviations: L. pneum. = Lobar pneumonia.

Bilat. O. M. A. = Bilateral acute otitis media.

Adm. B. C. H. = Admitted to Boston City Hospital.

Disch. = Discharged from Boston City Hospital.

Roman numerals represent pneumococcus types.

S. H. = Beta hemolytic streptococci.

throughout this study, while the other three had had "colds" lasting from one day to two weeks.

The 10 members of this family from whom type V pneumococci were cultured all had high titers of protective antibodies against this organism in their serum. The titers ranged from 10,000 to 1,000,000 fatal doses per 0.2 c.c. of serum. (Helen had a higher titer immediately after specific serum therapy.) In seven of the 10, agglutinins for the same type were also demonstrated in the same samples of serum. The agglutinin titers, except in two of the pneumonia cases, were very low.

In addition to the type V, other types of pneumococci were also cultured. Type VI pneumococci were first isolated from one of the children (Ruth) who had pneumonia. Subsequently, they were obtained from the throats of the father and of four other children. Type VI pneumococci were isolated from a culture of the father's throat taken several days before the one from which the type V organisms were obtained. Type VI pneumococci were found together with type V in John's second throat culture, the first culture having yielded only the latter type. In the other individuals, these two types occurred simultaneously. The relation of the type VI pneumococci to the colds can not be determined from the available data, but this type could not be found in the aural discharge of any of the children with suppurative otitis media. Type XIX pneumococci were cultured from the youngest member of the family, Arthur, who had had a mild infection three weeks previously. Type III pneumococci, together with type V, were isolated from the pharynx of the mother, Helen Sr., on two occasions. Agglutination tests with types III, VI and XIX pneumococci were done in each instance but failed to show agglutinins for these types in any of the sera. No serum was available from the infant, Arthur, who was the only member of the family from whom type V pneumococci were not recovered.

In addition to the pneumococci, beta hemolytic streptococci were cultured from several members of the family. A few colonies of this organism were first noted in the throat culture of Ruth while she was in the hospital. Two weeks later, these organisms were found in small numbers in the pharyngeal cultures of the mother and of one of the brothers (Vincent), but pneumococci predominated in these cultures. On the following week, the hemolytic streptococci were again cultured from the mother and from Ruth, but at this time the latter had tonsillitis and the streptococci were obtained from her in almost pure culture. On the same day, these organisms were cultured for the first time from four other members of the family, including the father, who had a sore throat at the time, and Helen, who had been discharged from the hospital one week previously and had developed tonsillitis since her return home. The strains of hemolytic streptococci were not identified serologically.

TABLE II
Epidemiological Observations

Ruth.....	Sickly all year. Home from school Apr. 4 to 12 because of cough. Taken to and from school daily by a milk attendant, aged 76 years, who developed "double pneumonia," on Apr. 14 and died Apr. 28 (etiology not determined).
Helen.....	Slept with David and Nancy until Apr. 27 (with David on Apr. 27). Visited uncle on Apr. 25. Had previously helped care for uncle's children, 3 of whom had otitis media and 2 had mastoidectomies (cultures showed hemolytic streptococci).
David.....	Slept with Helen. Played with Ruth.
John.....	Slept with Vincent Apr. 27. Slept with David 1 night.
William.....	Visited children frequently at hospital, also helped to care for other children at home.
Nancy.....	Slept with Helen on Apr. 25 and 26.
Helen, Sr.....	Nursed all the children while at home. In bed only a few hours during acute stage of "cold," May 2 to 3.
Mary.....	Slept with Ruth Apr. 25, 26 and 27. On Apr. 25 and May 2, visited uncle (cf. Helen).
Vincent.....	Slept with John until May 2. Helped care for David and Helen until Apr. 28.
Margaret.....	Alternately slept with Nancy and David.

EPIDEMIOLOGICAL OBSERVATIONS (TABLE 2)

The degree of contact among the members of this family was found to be extreme, although their living conditions were fairly good and they occupied a comfortable home in the outskirts of the city. Naturally enough, all the younger children played together to some extent. Ruth slept in the same bed with Mary. Both developed acute otitis media and Ruth also developed pneumonia. Helen slept with Nancy and with David during the early part of this outbreak. David also slept with John who, in turn, slept with Vincent on other occasions. John, David, Helen, Mary and Vincent all had otitis, while Helen and Mary acquired lobar pneumonia as well. The parents and the older children waited on the sick members of the family at home and the father visited the children at the hospital regularly. The possibilities of spread by direct contact are evident.

The attempts to elucidate an outside source of infection were not altogether fruitful. Ruth was the first to become ill. She was a deaf mute who attended a special school of 200 pupils, none of whom had had any recent significant respiratory or middle ear infections. However, a woman, aged 70, who acted as a milk attendant at the school developed symptoms of pneumonia on April 14 and died on April 28. She had accompanied Ruth and five other children to and from school daily until April 14. None

of the other children had any illness during April. The onset of the first infection in the family occurred in Ruth on April 16.

The only other reasonably possible outside source of infection was the family of an uncle, three of whose children had had "running ears" for a long time and two had had mastoidectomies. All, apparently, had recovered completely several weeks previous to Ruth's illness. Both Helen and Mary had visited at the uncle's home during the illness of their brothers and sisters, and Helen had previously helped care for some of her cousins when they were ill. The purulent, aural and mastoid discharges of the cousins had been cultured and had yielded hemolytic streptococci. Unfortunately, no bacteriological studies were made of the pneumonia in the milk attendant.

COMMENT

Previous reports of epidemics of pneumococcus infections have been limited, for the most part, to outbreaks of pneumonia due to type I or type II pneumococci. Schroder and Cooper⁵ reported an institutional outbreak during which type V pneumococci were cultured from seven of the nine cases of pneumonia which were investigated. Associated with these pneumonias was a high incidence of "colds" and bronchitis in the institution, but the individuals with these conditions were not studied bacteriologically. Among the cases of multiple contact infections reported by Tilghman and Finland,⁶ six groups were due to types of pneumococci segregated by Cooper¹ from among those previously included in Group IV. It is clear from these recent studies and from the present report that pneumococci other than types I and II may be disseminated by direct contact with cases or carriers and produce disease.

One of the families previously reported³ bears many resemblances to the present one. Family "P." consisted of 13 members, nine of whom either developed pneumonia or otitis media due to type V pneumococci or became healthy carriers of this organism. Subsequently, seven members of this family became carriers of type XXII pneumococci either with or without manifestations of infections due to this organism. Of the nine individuals from whom type V pneumococci were isolated, eight had specific antibodies for this organism in their blood, and these eight included three healthy carriers. Among the seven members from whom type XXII pneumococci were cultured, four had agglutinins for this type; two of the latter were entirely free of infection. One later had tonsillitis and only hemolytic streptococci were cultured from his throat at the time of this infection. The course of this outbreak is shown in figure 2.

The immunological observations in the family reported in this paper and those in the families previously studied³ indicate that healthy contact carriers of disease producing pneumococci acquire antibodies for the types of pneumococci which they carry. Similar observations were made by Harris and Ingraham.⁴ Types of pneumococci which were found without

reference to infections were not associated with homologous circulating antibodies. This was true in the present family, and in the families previously studied.³

The etiological relationship of the various pneumococci found in the throat to the "colds" and bronchitis which were observed is difficult to evaluate. Presumably the common colds were due to filterable viruses. The presence of these colds, however, apparently provided favorable conditions for the propagation and rapid dissemination of these pneumococci and probably aided in the establishment of infection with the more virulent

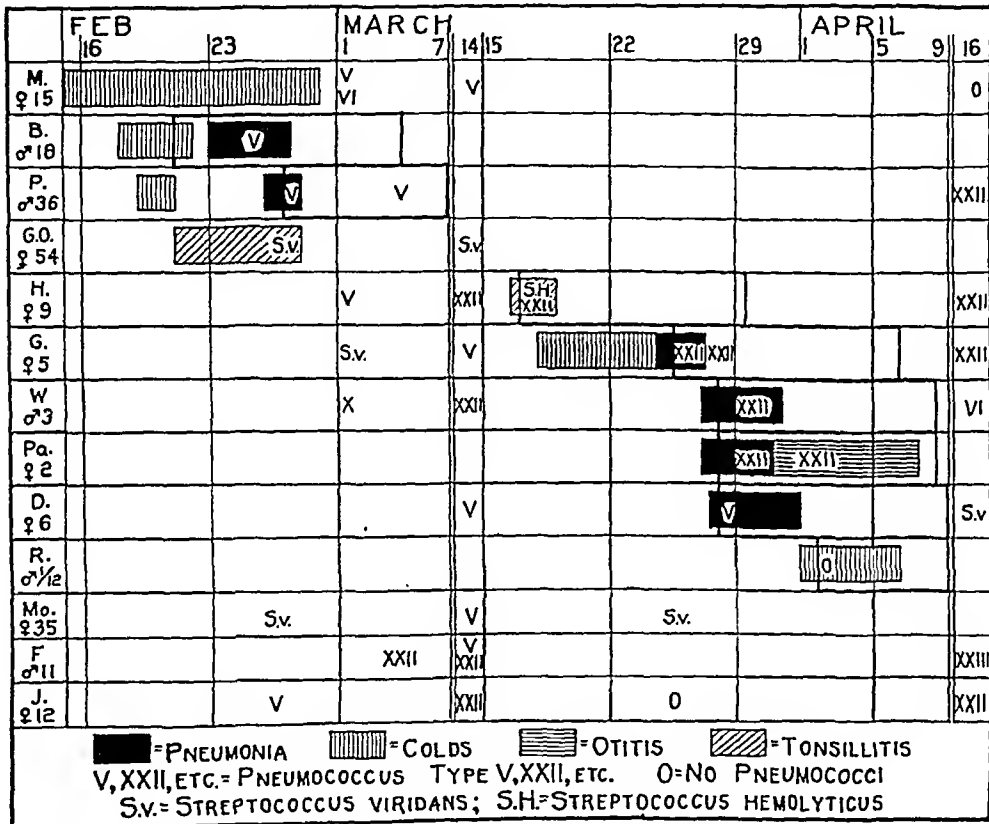


FIG. 2. Respiratory infections in family P. Heavier lines enclose the interval of hospitalization.

type. None of the infections could be definitely attributed to the type VI pneumococci. Previous studies have indicated that the blood of normal children and adults almost universally has marked pneumococcidal activity against type VI pneumococci and the serum is frequently capable of protecting against many fatal doses of these organisms. Such natural antibodies against type V pneumococci are comparatively uncommon.²

The sudden and simultaneous outbreak of four cases of pneumonia and otitis media due to type V pneumococci in one family suggests that the organisms in each of these cases were derived from a common source.

Whether this source was a carrier within the family or some case or carrier outside could not be ascertained from the available data. It is possible that Ruth had been exposed to type V pneumococci during her initial "cold" and the others had acquired the organism from her shortly thereafter. The two cases of otitis media that occurred in this family later were probably secondary cases arising out of exposure to the first group. These later cases occurred in the oldest children who presumably had less exposure than the younger ones.

SUMMARY

Clinical, bacteriological and immunological observations were made during an outbreak of "colds," otitis media and pneumonia affecting 10 of 11 members of one family. Type V pneumococci were obtained from the aural discharges in each of the five cases with suppurative otitis media and from the sputum or throat cultures in 10 members of the family, including the only member who remained free of infection. Antibodies for the homologous type were demonstrated in the serum of every member of the family from whom type V pneumococci were cultured, including the healthy contact carrier. During the course of this study type VI pneumococci were also isolated from six members of the family. No infections definitely attributable to this organism occurred, and agglutinins for this type were not demonstrated in any of the sera. Towards the end of the outbreak, hemolytic streptococci were cultured from the throats of seven members of the same family. Of these, two developed tonsillitis and one had a "sore throat."

REFERENCES

1. COOPER, G., ROSENSTEIN, C., WALTER, A., and PEIZER, L.: The further separation of types among the pneumococci hitherto included in Group IV and the development of therapeutic antisera for these types, *Jr. Exper. Med.*, 1932, 1v, 531.
2. FINLAND, M., and SUTLIFF, W. D.: Immunity reactions of human subjects to strains of pneumococci other than types I, II and III, *Jr. Exper. Med.*, 1933, 1vii, 95.
3. FINLAND, M., and TILGHMAN, R. C.: Bacteriological and immunological studies in families with pneumococcic infections: The development of type-specific antibodies in healthy contact carriers, *Jr. Clin. Invest.*, 1936, xv, 401.
4. HARRIS, A. H., and INGRAHAM, H. S.: A study of the carrier condition associated with Type II pneumonia in a camp of the civilian conservation corps, *Jr. Clin. Invest.*, 1937, xvi, 41.
5. SCHRODER, M. C., and COOPER, G.: An epidemic of colds, bronchitis and pneumonia due to Type V pneumococci, *Jr. Infect. Dis.*, 1930, xlvii, 384.
6. TILGHMAN, R. C., and FINLAND, M.: Pneumococcic infections in families, *Jr. Clin. Invest.*, 1936, xv, 493.

ELECTROCARDIOGRAPHIC OBSERVATIONS IN CARDIAC SURGERY *

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PROMPTED by recent developments in cardiac surgery we have investigated, from an electrocardiographic point of view, the effect of surgical manipulation of the heart, both during and after operation. This study is based upon a series of 32 patients all of whom were operated on by Dr. Claude S. Beck. The operations were of two types. The first operative group comprised cases of cardiac anastomosis,¹ for angina pectoris and coronary sclerosis, of which there were 24 cases. The second group were cases of resection of compressive pericardial scars² for chronic cardiac compression (Pick's disease), of which there were eight cases, one of which was operated on twice.

METHOD

Electrocardiograms were taken before the operation and at various intervals during the surgical procedure. The three standard leads were taken ordinarily, but in some instances only one lead (usually Lead II) was recorded because of the rapidly progressing surgical procedure. The string shadow was watched during most of the non-recording periods. In the more recent cases accurate time was kept with each record so that correlations with the anesthetist's chart could be made. In all cases the exact step in the operative procedure was noted.

Patients were given morphine and atropine by hypodermic injection from one to one and a half hours before operation. One anesthetist (Mrs. G. Fife) administered the anesthesia in all operations. Nitrous-oxide-oxygen-ether anesthesia was used in 31 operations, supplemented by avertin in six. Cyclopropane with avertin was used twice and procaine (locally) with nitrous-oxide-oxygen-ether anesthesia was used once. In 24 of the cases, an oxygen tent was used postoperatively.

As a preface to this study, the effect of anesthesia in itself must be considered. Kurtz, Bennet and Shapiro³ found in 109 patients that cardiac arrhythmias were commonly encountered during various non-cardiac operations. The depth and duration of anesthesia had no influence on the arrhythmias. Disturbances of rhythm occurred at all stages of operations and were frequently noted during the preparation of the operative field before the incision was made. Eight of their cases showed delay in A-V conduction; two showed complete heart block; one, paroxysmal auricular

* Received for publication September 19, 1938.

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fibrillation; four, multiple focus ventricular tachycardia; 20, auricular extrasystoles, and 32, ventricular extrasystoles. Patients with abnormal hearts had more changes than patients with normal hearts. The highest incident of arrhythmias occurred with chloroform and the lowest with procaine.

With these findings in mind, we question whether our abnormal electrocardiograms are the result of the anesthetic or whether they may be attributed directly to surgical manipulation of the heart.

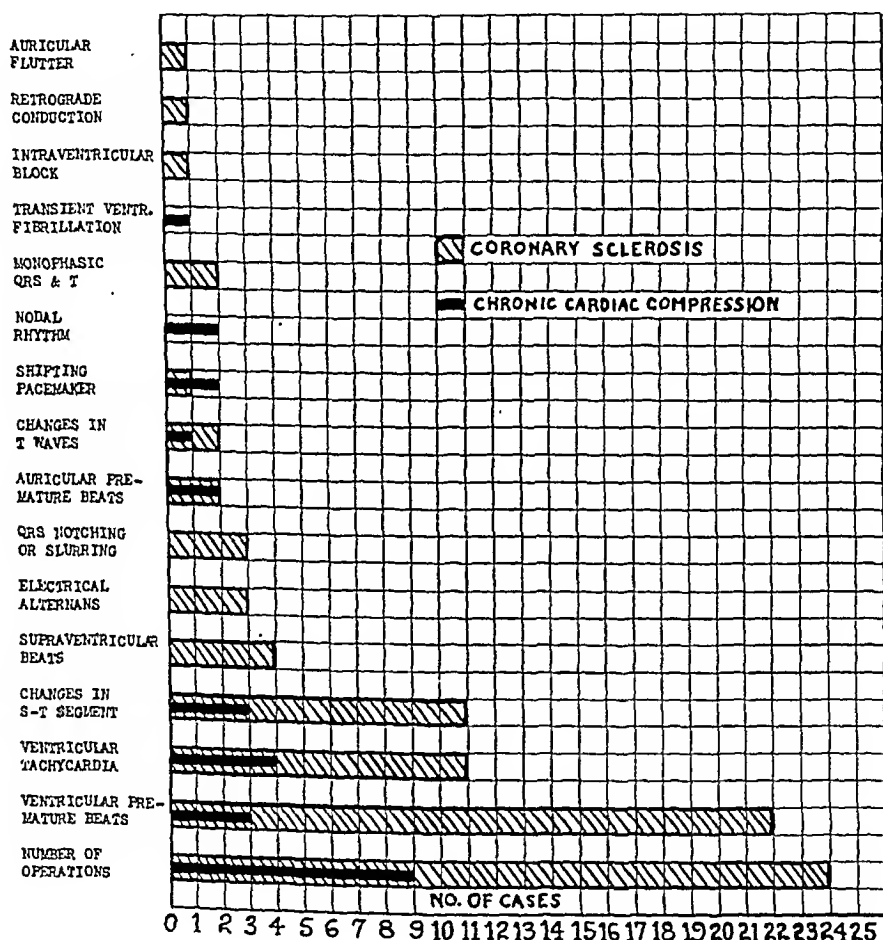


FIG. 1. Abnormal electrocardiographic findings during operation.

Premature beats are the response of cardiac muscle to abnormal irritation or stimulation. In the cases of compression the irritation is due to the separation of scar tissue from the epicardium by the delicate dissection. The irritation is much less than in the case of a cardiac anastomosis where it is due to the roughening of the epicardium with a burr, the insertion of bone meal and the grafting of muscle or fat upon the heart. Figure 1 illustrates all of the abnormal mechanisms found during each type of operation. In the operations for cardiac anastomosis isolated ventricular

premature beats, ventricular tachycardias, and changes in the position of the S-T segment predominate. Ventricular tachycardias include beats of unifocal as well as of multifocal origin (figure 3c). Isolated ventricular premature beats occurred in 22 out of 24 cases (91.7 per cent); there were 11 cases each (45.8 per cent) of ventricular tachycardias and S-T deviations. Of less frequent occurrence were supraventricular beats, auricular extrasystoles, notching and slurring of QRS complexes, changes in the T-waves, electrical alternation (figure 2B), shifting pacemaker, monophasic QRS complexes (figure 8C), intraventricular block (figure 8A), retrograde impulse conduction (figure 2A) and auricular flutter.

During the resection of compression scars, ectopic ventricular beats did not occur as frequently, probably because the irritation was less severe.

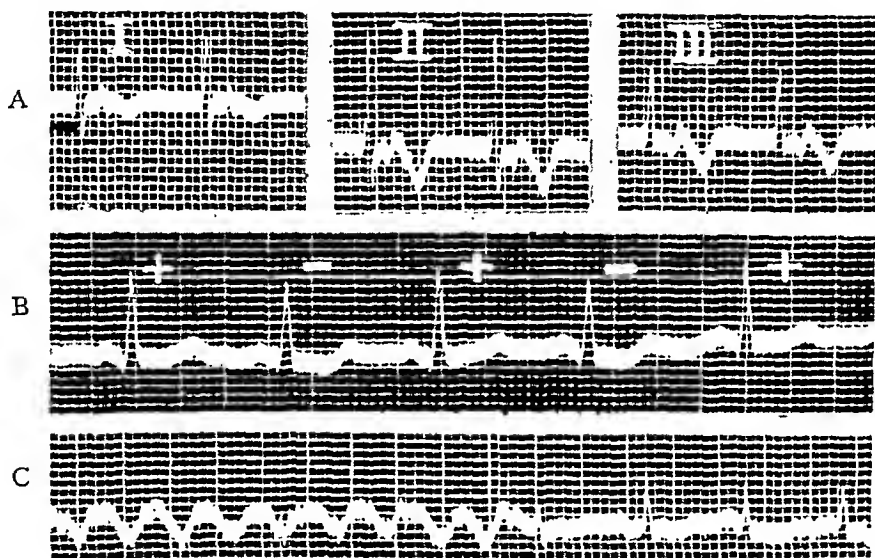


FIG. 2A (Case 26, J. C.). This patient, a man, aged 36, was not given quinidine. Pericardiectomy was performed under gas-oxygen-ether anesthesia. No procaine was used. Leads I, II, and III show a nodal rhythm with retrograde impulse conduction. The P-waves interrupt the S-T segment. This record was taken when the pericardial scar was partly resected and the heart was starting to bulge through the opening. In subsequent records, regular sinus node impulses, at times took over the rhythm.

B (Case 23, C. Z.). This patient, a man, aged 48, was given 13 grains (0.84 gm.) of quinidine preoperatively and a cardiac anastomosis was performed under avertin-ether anesthesia. The pericardium had just been opened and sutured to the chest wall when this record (Lead I) was taken. Procaine had not yet been applied. The R-waves alternate in amplitude. Diphasic T-waves are concordant with the smaller R-waves. Alternation also occurred in Lead II, but not in any of the other records taken on this patient.

C (Case 28, A. P.). This patient, a woman, aged 42, was given 7 grains (0.45 gm.) of quinidine preoperatively and a pericardiectomy was performed under gas-oxygen-ether anesthesia. During a rest period this record (Lead III) of transient ventricular fibrillation was obtained. A sinus rhythm ends the fibrillation abruptly. No procaine was used.

Ectopic auricular beats, shifting pacemaker and nodal rhythm occurred twice in each group. Deviations in the S-T segment occurred in three instances and changes in the T-waves occurred once. Figure 2C shows a transient ventricular fibrillation which occurred in one case.

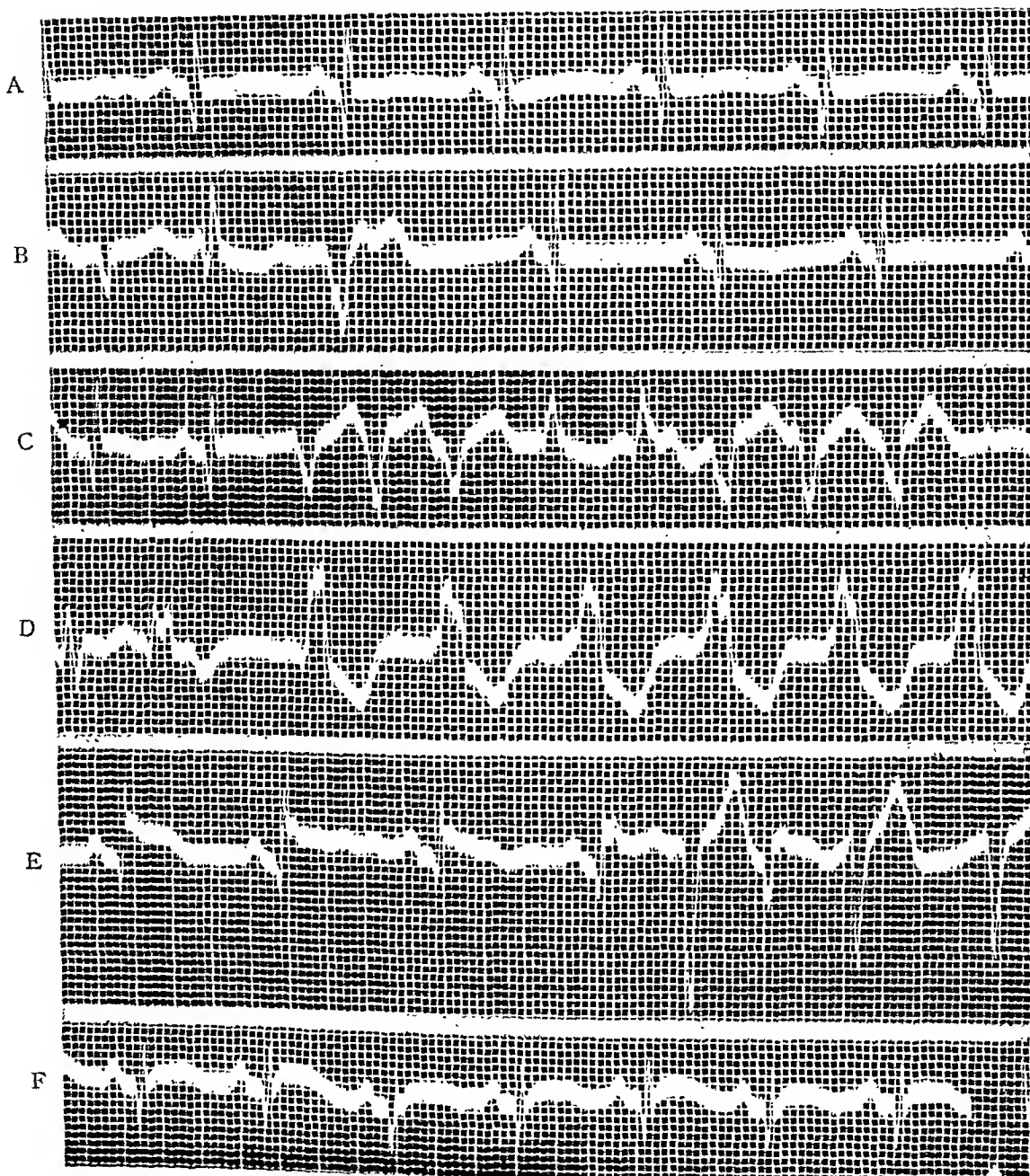


FIG. 3 (Case 24, J. F.). This patient, a man, aged 51, was given 12.5 grains (0.81 gm.) of quinidine preoperatively. A cardiac anastomosis was performed in April 1937 under avertin-cyclopropane anesthesia. All records are of Lead II. This patient had had a coronary occlusion in November 1933 and another in August 1936.

A. Control at 8:58 a.m. before cyclopropane intratracheal anesthesia. The Q_2 and a deep Q_3 (not illustrated) are probably due to a remote cardiac infarct.

B. Pericardium opened, 9:54 a.m. Record shows three ectopic ventricular beats. At 9:58 a.m. 2 c.c. of 5 per cent procaine were applied to the surface of the heart.

C. Posterior parietal pericardium burred, 10:04 a.m. Record shows a ventricular tachycardia due probably to two different foci of impulse initiation. This occurred even though procaine had been applied.

D. Left ventricle anteriorly and laterally burred, 10:09 a.m. Record shows premature ventricular beats from different foci followed by a probable nodal rhythm with intra-ventricular block.

E. Posterior surface of the heart burred, 10:15 a.m. There are three ectopic ventricular beats. The S-T segment is elevated 4 mm. This may either be a procaine effect or due to myocardial damage.

F. Closure, 10:30 a.m. Record is similar to control except for cove shaped S-T segment. As mentioned under E, this may be due to procaine or myocardial damage.

In the report of 109 non-cardiac operations, extrasystoles of various origins, displaced pacemaker and sinus arrhythmia predominated. According to Wachsmuth and Eismeyer,⁴ operative manipulation (non-cardiac in nature) is of much less importance than the anesthetic in the production of cardiac irregularities. They studied the electrocardiograms in dogs and humans during surgical procedures. Hill,⁵ Maher, Crittenden and Shapiro⁶ as well as Kurtz et al.³ were also unable to correlate surgical manipulation with cardiac response.

Figures 4A and 4B show the incidence of ventricular premature beats and of ventricular tachycardias during the various stages of the heart operation. In some patients both these mechanisms occurred; in others, neither one. In nine of the coronary cases, ventricular tachycardia occurred only during the period of cardiac manipulation. The latter period is that part of the operation during which the surgeon handles the heart, removes the epicardium or tears it in shreds, inserts bone meal and attaches the grafts. Twenty-one out of 24 (87.5 per cent) of the coronary cases showed isolated ventricular premature beats during this manipulation of the heart. In nine instances these premature ventricular beats occurred when the parietal pericardium was opened. Figure 3 illustrates typical electrocardiograms taken during the operative procedure. Figure 4C shows that in the coronary patients there is a gradual increase during operation of the other cardiac irregularities. This group of arrhythmias includes auricular and nodal premature beats, auricular flutter, wandering pacemaker, electrical alternation and transient ventricular fibrillation. In addition, notching of QRS and intraventricular block occurred.

Surgical manipulation in the cases of chronic cardiac compression causes few ectopic ventricular beats. The one case showing ventricular tachycardia at the end of the operation had only a few isolated ventricular premature beats during the operation. The compressed heart cases (figure 4C) showed that the other cardiac arrhythmias occurred in seven out of nine cases (77.8 per cent) during the period of cardiac manipulation.

In the operation of cardiac anastomosis, the preponderance of ectopic ventricular beats during the period of cardiac manipulation is obvious (figure 3 and figures 4A and 4B). One may conclude that in the latter operations, isolated ventricular premature beats and ventricular tachycardias are directly related to the manipulation of the heart by the surgeon. Other irregularities may be so related but a larger series of patients must be studied before a positive relationship can be demonstrated. The effect of drugs in preventing these irregularities will be discussed below.

Figure 4D illustrates the changes in the T-waves during operation. These changes consist in the transformation of upright waves to inverted or diphasic waves or vice versa. Once a change occurred it was not replotted in subsequent columns unless there was further change in the way of progression from or regression to the control status. This accounts for the low incidence of T-wave changes during the manipulation period,

whereas in reality, as compared to the control record, there is gradual increase in these changes. They are greatest after the operation has been completed (figure 6) because an inflammatory reaction takes place on the surface of the heart and cardiac damage is being repaired. In only four instances were the T-waves at the end of operation different from those of the control at the start of the operation. Most of the T-wave variations

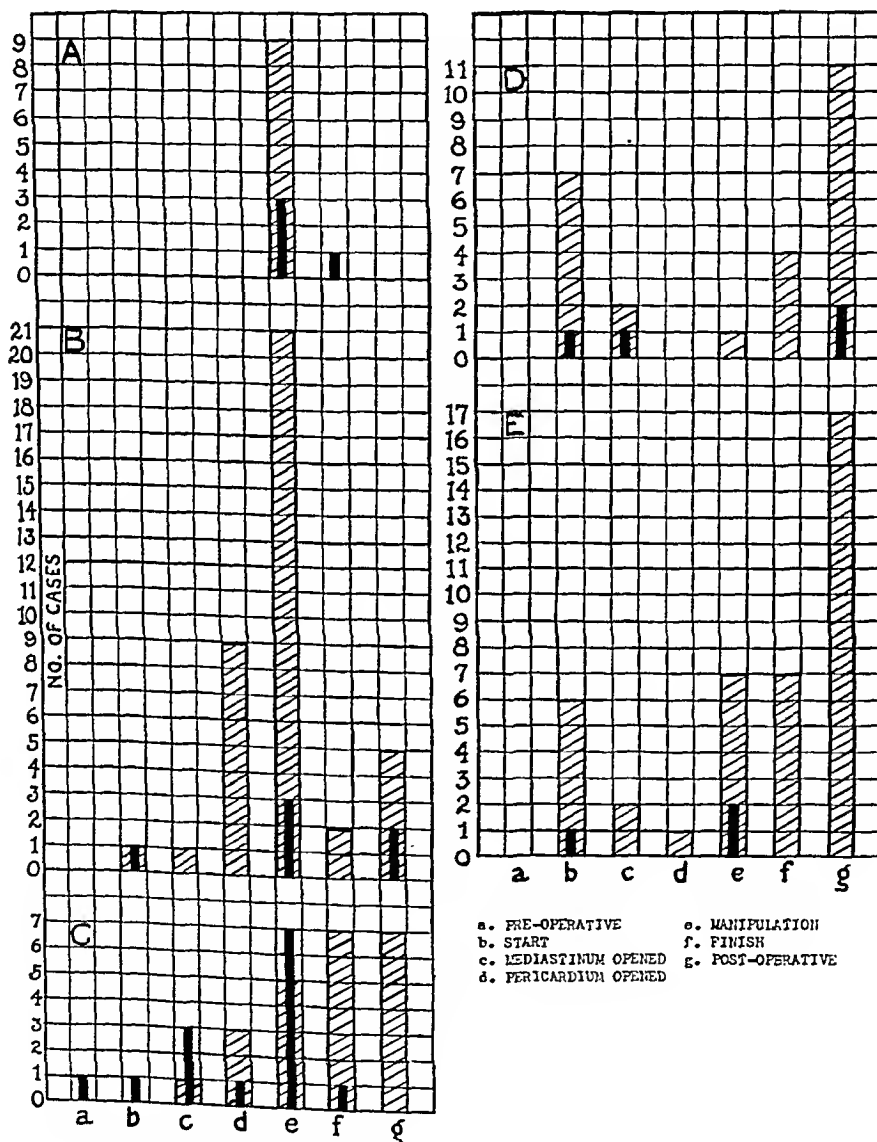


FIG. 4. Incidence of abnormal electrocardiographic findings during the various stages of the operative procedure. Cross-hatched bars indicate the number of cases of coronary sclerosis. Solid black bars indicate the number of cases of chronic cardiac compression.

- A. Ventricular tachycardia.
- B. Isolated ventricular premature beats.
- C. All other changes except D and E.
- D. Changes in T-waves.
- E. Changes in S-T segment.

are transient; many are associated with S-T changes which take place post-operatively.

Changes in the S-T segment consist in elevations or depressions from the isoelectric level. As in the case of the T-waves, only changes were plotted, as is shown in figure 4E. Experimental^{7, 8} as well as clinical^{9, 10} experience has shown that changes in the S-T or R-T segments are indicative of ventricular myocardial ischemia or damage. These deviations occur when the heart is roughened by the burr and irritated by the bone meal and grafts. Most changes occur postoperatively (figure 6) and are evidence of an acute myocarditis following operation. It is upon the establishment of this inflammatory reaction with the formation of capillaries, that the anastomosis of the blood supply of the graft with that of the heart in part depends.

The rather frequent S-T deviations at the start of the operation are probably due to anoxemia during the induction of anesthesia and to the added cardiac strain at this time. Six (25 per cent) out of 24 operations for coronary sclerosis and one (11 per cent) out of nine operations for chronic cardiac compression showed S-T variations at the start of the operation.

T and S-T changes during resection of compression scar are infrequent. The hearts in these cases usually have a good blood supply because the patients are younger than the patients with coronary sclerosis. Besides, the surgical trauma is less severe.

Sinus arrhythmias were of frequent occurrence in the records of Kurtz and his associates.³ We found none. The probable explanation lies in the fact that with rapid heart rates, sinus arrhythmia usually does not occur. In all but four of this series the auricular (sinus node) rate was 100 beats per minute or more. In the four, the auricular rate varied from 71 to 95.

Three patients of the compressed heart group showed no ventricular abnormalities during operation. One of these maintained a regular sinus rhythm with a heart rate of 110 to 120 beats per minute. Another showed no changes in rhythm or contour of the electrocardiographic complexes. The latter two had been given quinidine preoperatively. The third showed auricular extrasystoles, a wandering pacemaker with transient retrograde impulse conduction, S-T₂ depression, but no ventricular abnormalities. (No quinidine had been administered.)

A direct comparison of control records at the start of operation with records at the end showed that 14 out of 33 cases (42.4 per cent) were practically identical (rate excluded). In eight cases (26.2 per cent) the records were similar but not identical due to slight variations in the contour of complexes. The remaining 11 cases (33.3 per cent) showed definite changes as regards notching of QRS complexes, direction of P- and T-waves, position of S-T segment, and nodal and ventricular arrhythmias. These changes in detail are shown in table 1.

TABLE I.

Changes in Electrocardiograms at the End of Operation as Compared to Control Records

Case No.	
7, J. H.....	S-T _{1, 2} became depressed.
9, G. B.....	S-T _{1, 2} depression became isoelectric. Diphasic T _{1, 2, 3} became upright.
10, M. P.....	T ₁ became inverted.
15, W. R.....	Diphasic T ₁ became inverted, S-T ₂ became elevated.
17, A. C.....	R ₂ became notched.
18, L. H.....	Depressed S-T ₂ became almost isoelectric.
24, J. F.....	QRS became notched, S-T _{1, 2} became cove shaped, S-T ₃ became elevated, T-waves vary with the S-T deviation.
25, J. M.....	S-T _{1, 2} became elevated, Inverted P ₂ became upright.
26, J. C.*.....	Normal rhythm became nodal rhythm with re- trograde transmission.
28, A. P.*.....	Isoelectric P-waves became upright.
29, H. T.*.....	Rhythm of auricular fibrillation became a ven- tricular tachycardia.

* Cases of chronic cardiac compression.

A comparison of the heart rate as obtained from the electrocardiogram with that as reported by the anesthetist showed wide variations. In most cases the graphic record showed higher rates due to the fact that weak contractions were not transmitted to the peripheral pulse (figure 7). In a few instances, however, the anesthetist's rate was higher. This occurred at very rapid heart rates (135-145).

EFFECT OF PREOPERATIVE MEDICATION

The electrocardiographic changes in conjunction with cardiac operations have just been discussed and the relationship of premature beats and ventricular tachycardia to surgical manipulation of the heart mentioned. As is well known, extrasystoles and ventricular tachycardia may be classed as prefibrillation arrhythmias.

Ventricular fibrillation and coronary disease are closely related. This is probably best shown by the frequent occurrence of fibrillation following experimental as well as clinical coronary closure. Extrasystoles and ventricular tachycardia are also frequently found in patients with acute myocardial infarction. Since these two phenomena are so closely related to the operative procedure in cardiac surgery, the sudden onset of ventricular fibrillation at the operating table as well as post-operatively, is the constant fear of the surgeon. As a protection to the heart against fibrillation the use of quinidine systemically was instituted following observations in the experimental laboratory by Mautz.¹³

Quinidine depresses contractility, prolongs the refractory period, and conduction. The latter effects have long been used to combat auricular fibrillation. Scott¹¹ by continued administration of quinidine was able to

arrest and prevent ventricular tachycardia. Levine and Fulton¹² report similar findings. Nathanson¹⁴ showed that prefibrillation rhythms induced in elderly persons by intravenous injection of epinephrine could be prevented by the use of quinidine.

Twenty of the cases of coronary sclerosis can be divided into two groups of ten each. Group one received no quinidine preoperatively, and group two did receive quinidine preoperatively. In the latter group procaine hydrochloride was used as a local anesthetic on the heart at operation, but for this study only the electrocardiograms taken before procaine, were used.

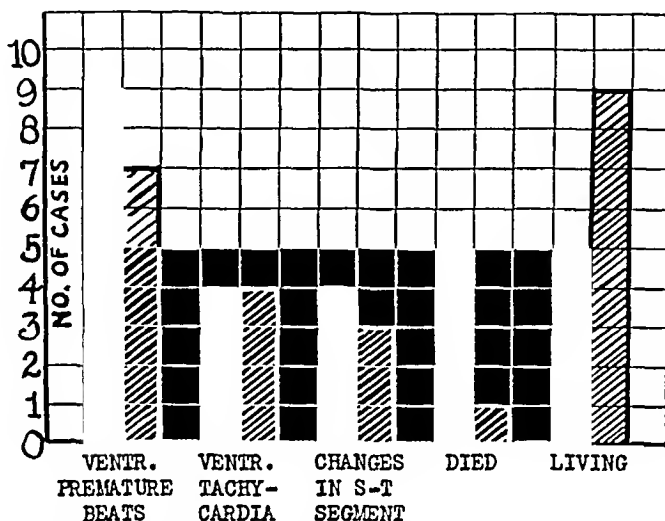


FIG. 5. Abnormal electrocardiographic findings during operation and mortality rate in cases of coronary sclerosis. Solid black bars indicate patients who did not receive quinidine preoperatively. Cross-hatched bars indicate patients who did receive quinidine preoperatively.

Figure 5 shows that there is little difference between the two groups. One cannot say that quinidine, as far as this study is concerned, has a demonstrable effect in preventing prefibrillation arrhythmias. The mortality rate on the other hand appears reduced by the use of quinidine. Is this due to the protection of the heart by quinidine against fibrillation? In this method of establishing a new blood supply to the heart, the magnitude of the operation has been reduced in the more recent cases by the use of a unilateral approach, by the use of smaller grafts, by the use of ground bone instead of extensive excoriation to set up an inflammatory reaction, and also by the use of internal drainage into the left pleural cavity to prevent cardiac tamponade.¹⁶ The rôle that each of these factors plays, as well as the choice of better risk patients must all be considered. As far as the anastomotic operations are concerned each of the above procedures appears to have been an improvement and influential in reducing the risk of operation. Even though we cannot prove by means of electrocardiograms that the number of prefibrillation arrhythmias has been reduced, clinically, there seems to have been a beneficial result.

During the removal of the scar in one patient with chronic cardiac compression, Dr. Beck noticed a transient period of incoordinated ventricular activity which (figure 2C) proved to be a fleeting ventricular fibrillation. This occurred while he dissected a scar from the descending ramus of the left coronary artery which in turn probably reduced the amount of blood going through this artery. This patient had been given 7 grains (0.45 gm.) of quinidine sulphate preoperatively. In another compressed heart case the patient suddenly died seven hours after operation. This

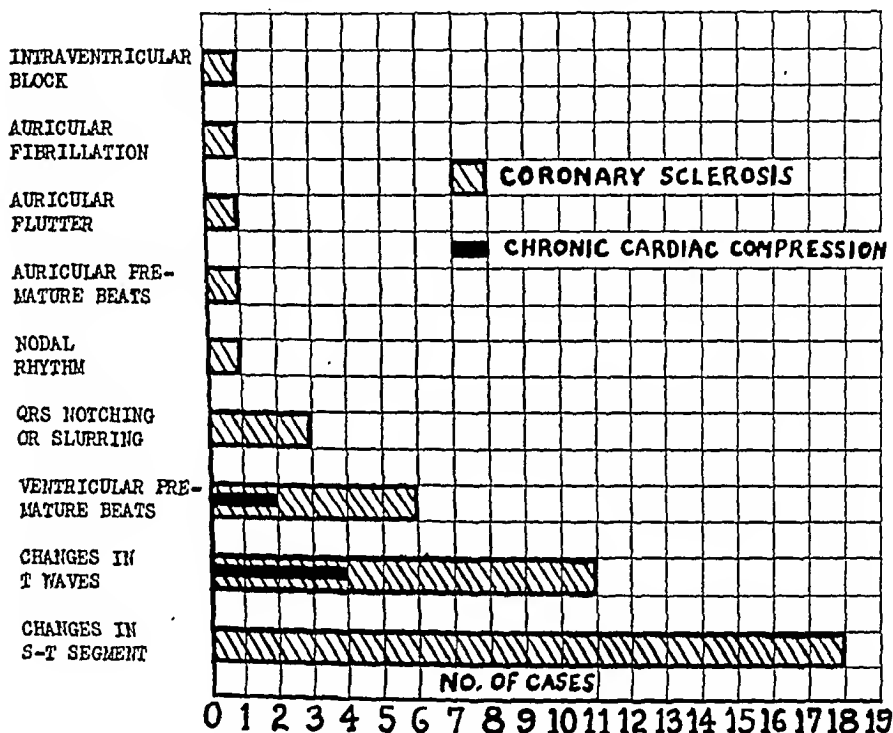


Fig. 6. Abnormal electrocardiographic findings post-operatively.

patient was not given quinidine. Dr. Beck suggested that the cause of death was related to dilatation that occurred when the small atrophic heart was relieved of its compression.

EFFECT OF LOCAL ANESTHETICS APPLIED TO THE CARDIAC SURFACE TO REDUCE CARDIAC IRRITABILITY

Mautz¹⁸ has shown experimentally that the surface irritability of the heart can be decreased by local application of metacaine and procaine. The maximal effect develops within five minutes. On the basis of experimental effects, procaine is used by Dr. Beck in human cases. Two c.c. of a 5 per cent solution are diffused upon the surface of the heart. If this is not effective it may be injected into the cavity of the right ventricle whence it returns to the left ventricle and enters the coronary arteries.

Following the use of procaine in 10 patients, six showed no effect, i.e., there were as many extrasystoles and ventricular tachycardias after application as before. Figure 8B shows a ventricular tachycardia which occurred following the use of procaine. This patient was given a second application, following which no premature beats occurred and a monophasic ventricular complex was produced (figure 8C). These monophasic waves have been described by Mautz¹³ as due to the action of the anesthetic on the myocardium.

In three patients following the use of procaine, premature beats ceased. In one patient there were a few isolated premature beats whereas before procaine application there were runs of extrasystoles. The latter four

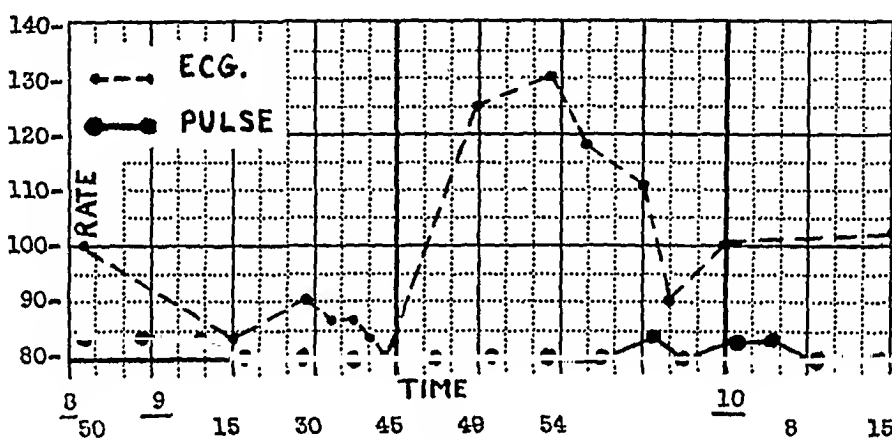


FIG. 7 (Case 23, C. Z.). Comparison of the heart rate as reported by the anesthetist and as obtained from the electrocardiogram. At slower rates the anesthetist's record usually falls below that of the electrocardiographic rate because many of the weaker premature beats are not transmitted to the peripheral pulse.

patients also showed stabilization of the blood pressure level following the use of procaine.

In evaluating the effect of procaine in these few patients, one must consider the different degrees of coronary sclerosis and myocardial ischemia in the various cases; the individual variations in irritability of the heart; the different degrees of surgical trauma, and variations in dosage of procaine. Perhaps a larger dose would have been effective in the six cases which showed no response but we are feeling our way in the use of this drug and we do not want to get toxic effects from large dosage. Conclusions had best be deferred until more cases are studied.

The above discussion shows that the electrocardiograph can point out to the cardiac surgeon those procedures which most disturb the heart and which, therefore, necessitate operative care. Experimentally, quinidine sulphate given systemically lessens the danger of auricular or ventricular fibrillation, and procaine reduces the irritability of the surface layer of myocardium at operation. A method of determining effective dosage is

necessary. For quinidine, Nathanson's¹⁴ method of using epinephrine to induce premature beats and quinidine to counteract this effect, might be used preoperatively in determining the dose. Unfortunately this method is dangerous for cardiac patients and especially in angina pectoris.

For procaine, the dosage is determined at operation. Toxic effects must be avoided.

It has been shown experimentally by Mautz and Beck¹⁵ that procaine introduced into the right ventricle reduces the irritability of the myocardium. This reduction in irritability is useful in throwing the ventricles out of fibrillation. They have worked out a method for defibrillation of the ventricles which in the dog is uniformly successful. This method should find an important place in all operating rooms, not only in heart operations

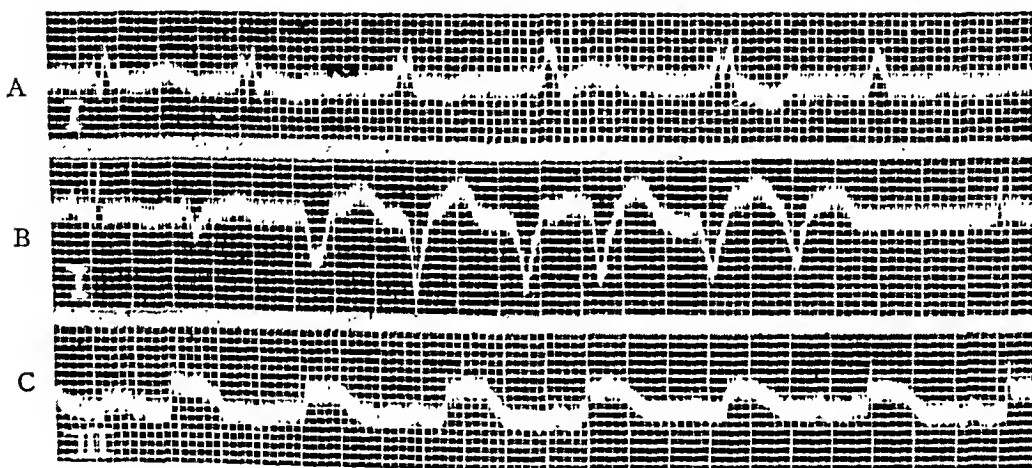


FIG. 8 (Case 25, J. M.). This patient, a man, aged 52, was given 12 grains (0.78 gm.) of quinidine preoperatively and a cardiac anastomosis was performed under avertin-cyclopropane anesthesia.

A. Lead I taken 19 minutes after an application of 2 c.c. of 5 per cent procaine to the heart. The epicardium over the conus arteriosus was being burred. The QRS complexes are notched, vary in contour and in duration (0.08–0.12 sec.). This period of intraventricular block was transient, it had disappeared by the time Leads II and III were taken. There are no definite P-waves and the T-waves vary in direction.

B. Lead I taken 25 minutes after the first procaine application (2 c.c. of 5 per cent) while a second application was being made. This record shows a ventricular tachycardia with beats originating in at least four different foci.

C. Lead III taken about a minute later shows a monophasic type of ventricular complex. This was also seen in Lead II. The S-T segment is elevated from 2 to 3 mm.

but also in operations upon other parts of the body when death suddenly supervenes.

CONCLUSIONS

1. The predominant electrocardiographic abnormalities found during operations for coronary sclerosis are: isolated ventricular beats, ventricular tachycardia, and deviations of the S-T segment from the isoelectric line.

2. During cardiac anastomosis, ventricular premature beats and ventricular tachycardias are directly related to the manipulation of the heart by the surgeon.

3. During the resection of compression scars, ectopic ventricular beats are not as frequent as in cardiac anastomosis because the irritation is less severe.

4. Most of the T-wave variations during cardiac anastomosis are transient; many are associated with S-T changes which take place post-operatively due to an acute pericarditis. T and S-T changes during resection of scars are infrequent.

5. The effectiveness of quinidine in preventing prefibrillation arrhythmias could not be conclusively demonstrated.

6. Procaine hydrochloride, as a local anesthetic applied to the surface of the heart during cardiac operations, may be of some use in preventing prefibrillation arrhythmias.

REFERENCES

1. BECK, C. S.: The development of a new blood supply to the heart by operation, *Ann. Surg.*, 1935, cii, 801.
2. BECK, C. S., and GRISWOLD, R. A.: Pericardiectomy in the treatment of the Pick syndrome, *Arch. Surg.*, 1930, xxi, 1064.
3. KURTZ, C. M., BENNET, J. H., and SHAPIRO, H. H.: Electrocardiographic studies during surgical anesthesia, *Jr. Am. Med. Assoc.*, 1936, cvi, 434.
4. WACHSMUTH, W., and EISMAYER, G.: Heart action as affected by operative procedures, *Deutsch. Ztschr. f. Chir.*, 1928, ccix, 145.
5. HILL, I. G. W.: The human heart, in anesthesia: electrocardiographic study, *Edinburgh Med. Jr.*, 1932, xxi, 533.
6. MAHER, C. G., CRITTENDEN, P. J., and SHAPIRO, P. F.: Electrocardiographic studies of viscerocardiac reflexes during major operations, *Am. Heart Jr.*, 1934, ix, 664.
7. SMITH, F. M.: Ligation of coronary arteries with electrocardiographic study, *Arch. Int. Med.*, 1918, xxii, 8.
8. CRAWFORD, J. H., ROBERTS, G. H., ABRAMSON, D. I., and CARDWELL, J. C.: Localization of experimental ventricular myocardial lesions by the electrocardiogram, *Am. Heart Jr.*, 1932, vii, 627.
9. PARDEE, H. E. B.: An electrocardiographic sign of coronary artery obstruction, *Arch. Int. Med.*, 1920, xxvi, 244.
10. PARKINSON, J., and BEDFORD, D. E.: Successive changes in the electrocardiogram after cardiac infarction, *Heart*, 1928, xiv, 195.
11. SCOTT, R. W.: Observations on a case of ventricular tachycardia with retrograde conduction, *Heart*, 1921, ix, 297.
12. LEVINE, S. A., and FULTON, M. N.: The effect of quinidine sulphate on ventricular tachycardia, *Jr. Am. Med. Assoc.*, 1929, xcii, 1163.
13. MAUTZ, F. R.: Reduction of cardiac irritability by the epicardial and systemic administration of drugs as a protection in cardiac surgery, *Jr. Thoracic Surg.*, 1936, v, 612.
14. NATHANSON, M. H.: Pathology and pharmacology of cardiac syncope and death, *Arch. Int. Med.*, 1936, lviii, 685.
15. MAUTZ, F. R., and BECK, C. S.: Control of heart beat by the surgeons with special reference to ventricular fibrillation occurring during operation, *Ann. Surg.*, 1937, cvi, 525.
16. BECK, C. S., and FEIL, H.: Consideration of the artificial development of collateral coronary circulation by surgical means, *Mod. Con. Cardiovasc. Dis.*, 1937, vi, 6.

THE VITAMIN C REQUIREMENT IN RHEUMATOID ARTHRITIS *

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IN normal healthy individuals the blood serum or plasma level and the urinary excretion of vitamin C are dependent largely upon the dietary intake of the vitamin.^{1, 2, 3, 4} It has been shown by van Eckelen⁵ and Heinemann⁶ that normal adults have a daily requirement of 60 mg. of the vitamin.

The presence of infection is known to increase the requirements for vitamin C.⁷ In patients suffering with various forms of infection the level of vitamin C in the blood plasma or serum may be reduced to the level found in patients with scurvy.⁷ Under these circumstances the amount of vitamin C required to raise the blood plasma level of the vitamin to that of the kidney threshold and to maintain this degree of "saturation" is many times that accepted as the normal requirement of healthy individuals.⁸

Rinehart^{9, 10} has shown that in patients with rheumatoid arthritis there is an apparent vitamin C deficiency as indicated by low concentration of the vitamin in the blood.

The present studies were originally undertaken to determine the incidence of lowered vitamin C content of the blood among patients with rheumatoid arthritis as compared with normal individuals on a similar dietary regime. At the same time information was sought which would indicate whether patients with rheumatoid arthritis had a greater requirement for vitamin C than normal people, and if so whether the satisfaction of such an increased demand would result in clinical improvement.

METHODS

Analytical. The method for the determination of cevitamic acid in the blood plasma is essentially that of Farmer and Abt¹¹ with slight modifications to prevent oxidation of the vitamin.

Five ml. of venous blood are withdrawn into a tube containing 0.05 ml. of potassium oxalate saturated solution and 1 drop of 5 per cent sodium cyanide solution. The blood is centrifuged and 2 ml. of the plasma are precipitated with 4 ml. of 5 per cent metaphosphoric acid and 4 ml. of distilled water. The protein is removed by either centrifugalization or filtration. Two ml. samples in duplicate of the filtrate are diluted with 3 ml. of distilled water and titrated with 2-6 dichlorophenol-indophenol solution

* Received for publication June 29, 1938.

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which had been standardized on the same day. The first pink color persisting for 30 seconds is arbitrarily taken as the end point.

The determination of cevitamic acid in urine is made according to the method of Taylor et al.¹²

Standard Solutions. The 2-6 dichlorophenol-indophenol solution is made up fresh every week. Approximately 20 mg. of LaMott special indicator solution are weighed into a 100 ml. volumetric flask, dissolved in hot boiled water and diluted to the mark with cold boiled distilled water. (The solution is usually complete, but if any insoluble material is present it should be removed by filtration.) This stock dye solution is then kept in the ice-box in a brown glass stoppered bottle.

The working standard is prepared by diluting 10 ml. of the stock dye solution to 100 ml. in a volumetric flask using freshly boiled distilled water.

Standardization of the Dye. Five hundred ml. of 2 per cent metaphosphoric acid are prepared by dilution with boiled distilled water. Approximately 15 mg. of cevitamic acid (Merck's Cebione) are weighed to four places on the analytical balance and transferred to a 100 ml. volumetric flask. The cevitamic acid is dissolved in 2 per cent metaphosphoric acid and diluted to the mark with the same reagent. Ten ml. of this stock standard are transferred to a second 100 ml. volumetric flask and made up to volume with 2 per cent metaphosphoric acid.

One ml. of this working standard is transferred to a titration flask and diluted with 4 ml. of 2 per cent metaphosphoric acid. The mixture is titrated with the dilute dye solution. A blank both for perception of end point and on reagents is made by titrating 5 ml. of 2 per cent metaphosphoric acid.

Clinical Material. The frequency of low levels of vitamin C in the blood plasma was determined from a study of 56 cases of rheumatoid arthritis. The cases were both early and late and had varying degrees of deformity and severity of symptoms. A control group of 12 normal adults living in the hospital on exactly the same diet was studied as a control. An intensive study of vitamin C metabolism was made in ten of the patients with rheumatoid arthritis of long duration. The vitamin C levels in the plasma of these individuals was less than 0.5 mg. per 100 ml. Four of these patients were placed on a vitamin C free diet for a period of from three to four weeks during which time urine analyses for vitamin C were made and periodic estimations of the amount of cevitamic acid in the circulating blood plasma. In addition the response of each of the four patients to the administration of a single oral dose of one gram of cevitamic acid was studied by following the changes in the level of the substance in the blood plasma and urine output of vitamin C. Daily red blood cell counts and hemoglobin determinations were made and the weights of the patients determined at frequent intervals. In addition close check was kept on any clinical changes in the patients including observations on the red blood cell sedimentation rate.

TABLE IA

Cevitamic Acid Level of Blood of 58 Unselected Cases of Rheumatoid Arthritis on Hospital Diet Containing Approximately 80 mg. per Day Cevitamic Acid

Patient No.	Age	Sex	Date	Cevitamic Acid mg./100 c.c. Blood Serum
1	44	female	June 14	2.320
2	27	male	Feb. 18	2.245
3	39	male	Feb. 17	2.023
4	57	female	June 2	1.650
5	40	female	Feb. 12	1.580
6	45	female	June 7	1.260
7	40	female	Feb. 12	1.260
8	49	female	May 6	1.160
9	37	female	Feb. 14	1.110
10	56	female	Feb. 18	1.035
11	29	female	Feb. 14	.950
12	39	female	Feb. 13	.890
13	51	female	May 21	.790
14	27	female	Apr. 27	.730
15	23	female	June 2	.720
16	47	female	Feb. 14	.700
17	50	female	June 18	.678
18	30	male	Apr. 22	.610
19	19	female	June 18	.604
20	62	female	June 18	.562
21	45	female	Apr. 23	.550
22	55	male	Feb. 16	.550
23	29	male	June 18	.548
24	19	male	Feb. 18	.521
25	30	male	May 12	.477
26	35	female	Mar. 10	.475
27	21	male	May 11	.465
28	57	female	Feb. 19	.450
29	13	female	Apr. 22	.429
30	42	female	Feb. 14	.420
31	22	female	Apr. 22	.401
32	23	male	Mar. 20	.393
33	27	female	Feb. 17	.362
34	41	female	May 12	.358
35	27	female	Mar. 20	.350
36	68	male	Apr. 21	.330
37	37	female	June 9	.329
38	51	female	Feb. 18	.329
39	57	female	Apr. 22	.321
40	18	female	Apr. 26	.317
41	61	female	Feb. 14	.302
42	70	female	June 2	.301
43	32	male	Feb. 18	.279
44	21	male	Feb. 20	.268
45	57	male	June 14	.257
46	27	female	May 16	.254
47	41	female	Feb. 18	.253
48	38	male	Feb. 17	.218
49	25	female	Apr. 26	.234
50	47	female	Apr. 27	.214
51	26	male	May 5	.193
52	41	male	May 5	.193
53	28	male	Apr. 27	.172
54	27	female	June 7	.158
55	27	male	Feb. 18	.152
56	17	male	Feb. 18	.152
57	23	female	Feb. 19	.150
58	50	female	May 12	.067

At the end of the control period each of the four patients was placed on a daily intake of 100 mg. of pure cevitic acid for two weeks and the various observations made during the control period repeated. The patients were then given 200 mg. of cevitic acid daily by mouth and the observations repeated.

In six of the ten patients the vitamin C free diet was replaced by an ordinary house diet on which the patients were maintained throughout the entire period of observation. In all other respects the studies on these cases were the same as on the other four.

At no time during the observations of any of the ten patients was there any abnormality in the basal metabolic rate and the patients' temperature showed the low fluctuations between 99 and 100° F. typical of the disease in its chronic stage.

EXPERIMENTAL RESULTS

The Incidence of Lowered Blood Plasma Cevitic Acid Level in Rheumatoid Arthritis. Observations on 24 cases were made shortly after admission to the hospital; the other 31 cases had been in the hospital for from one month to several years before the observations were commenced. The experimental data are summarized in table 1a. In summary, 14 or 25 per cent of these 56 patients showed a cevitic acid level in the plasma of 0.8 mg. per hundred ml. or higher, which is within the accepted normal range.⁴ Nine or 16 per cent had values between 0.5 and 0.8 whereas 33 or 59 per cent had levels of cevitic acid in the blood plasma below 0.5 mg. per hundred ml. Five of the patients who had plasma cevitic acid levels above 0.8 mg. had supplemented the hospital diet at the time of this survey with sufficient citrus fruits or orange juice to account for an additional intake of 80 mg. per day of cevitic acid.

TABLE 1b

Cevitic Acid Level of Blood of 12 Normal Individuals Maintained Exclusively on House Diet

Control No.	Age	Sex	Date	Cevitic Acid mg./100 c.c. Blood Serum
1a	24	female	May 10	2.066
2a	27	female	May 6	1.990
3a	54	female	Mar. 11	1.620
4a	56	female	May 5	1.470
5a	23	female	May 5	1.150
6a	36	male	May 10	1.150
7a	35	male	May 3	.929
8a	49	female	May 6	.832
9a	43	female	May 6	.785
10a	36	female	May 5	.680
11a	21	female	Feb. 16	.560
12a	26	male	May 10	.206

The data obtained on these 12 normal subjects are given in table 1b. Ten or 83 per cent had levels of cevitanic acid in the blood plasma ranging between 0.9 and 2 mg. per hundred ml. Two subjects had values of 0.6 and 0.25 mg. per hundred ml. respectively. The individual with the lowest plasma ascorbic acid stated that he rarely ate fruits or uncooked vegetables included in the diet.

TABLE II

Cevitanic Acid Level of Blood of 29 Cases of Rheumatoid Arthritis after Maintenance on Cevitanic Acid Therapy

Patient No.	Age	Sex	Date	Cevitanic Acid mg./100 c.c. Blood Serum	Cevitanic Acid Excretion in Urine mg./24 Hours	Mg. Cevitanic Acid Orally per Day	No. Days of Therapy
16	47	female	June 2	1.82	137.0	100	12
						200	11
						300	
20	62	female	June 18	.56	17.2	200	16
24	19	male	June 18	1.18	109.6	200	32
25	30	male	June 21	2.13	20.5	200	28
						100	13
27	21	male	June 24	1.32	118.3	200	41
28	57	female	June 24	1.19	87.5	200	14
30	42	female	Apr. 27	1.10	96.0	300	53
31	22	female	June 23	1.27	32.9	200	11
32	23	male	June 2	1.25	100.0	100	11
						200	12
33	27	female	June 22	1.12	104.8	200	39
37	37	female	June 24	1.72	42.0	200	41
38	51	female	June 22	1.83	73.3	100	11
						200	31
39	57	female	June 14	2.16	123.2	200	31
40	18	female	June 23	1.30	100.4	200	30
41	61	female	May 25	1.03	126.0	100	11
						200	12
						300	
42	70	female	June 19	1.71	72.6	200	35
43	32	male	June 18	1.12	144.9	200	33
46	27	female	June 9	1.18	121.4	200	25
49	25	female	June 21	.91	83.3	200	31
50	47	female	June 18	1.19	87.5	200	14
51	26	male	June 18	1.20	124.0	100	11
						200	32
52	41	male	June 26	1.30	36.5	100	11
						200	35
53	28	male	June 21	1.19	35.3	200	28
						100	10
54	27	female	June 21	1.51	148.8	200	14
55	27	male	June 21	1.60	44.2	200	28
						100	13
56	17	male	May 31	.84	139.0	100	11
						200	51
57	23	female	June 3	1.60	90.0	100	11
						200	35
58	50	female	June 18	.96			
10	56	female	June 21	1.30	23.0	100	11
						200	30

The data shown in tables 1a and 1b may be compared with those of table 2 which gives data for cases of rheumatic arthritis after the daily ingestion of vitamin C in amounts varying between 150 and 200 mg. per day. In all of these cases the blood level of vitamin C was normal.

The Vitamin C Requirements of Patients with Rheumatoid Arthritis. The four patients maintained on a vitamin C poor diet showed a daily excretion of vitamin C in the urine below 20 mg. The six patients whose control period was the ordinary house diet showed an excretion which did not exceed 50 mg. per day. During the control period no essential change was observed in the amount of vitamin C in the blood plasma.

The administration of 1 gram of vitamin C to these ten patients was followed by a prompt rise in the level of the vitamin in the blood which returned to the pre-administration levels in 48 hours.

All 10 patients were then placed on a daily intake of 100 mg. of vitamin C per day given in two doses and the urines analyzed daily for vitamin C. Blood samples were taken fasting and before the administration of the vitamin at frequent intervals. With the dosage of 100 mg. there was no significant rise in the blood cevitamic acid level during the two weeks of therapy above that of the control period, nor did the urine cevitamic acid rise remarkably above that obtained for the control period. A typical series of observations on one of these patients is shown in figure 2.

After the patients had taken for two weeks a dosage of 100 mg. per day they were given 200 mg. per day in four doses. Under these circumstances the blood levels rose progressively in 10 to 12 days reaching levels between 1.0 to 1.8 mg. per hundred ml. of blood and remained essentially constant. At the same time the daily urinary excretion increased markedly, ranging from 30 mg. to 100 mg. per day.

In three of the patients the vitamin C administered was increased by an additional 100 mg. The blood level of ascorbic acid did not increase beyond that obtained when 200 mg. were given each day but the daily urinary excretion was increased by 40 to 70 mg.

At the end of the period of 200 mg. level of administration vitamin C was omitted for two days and the response of the patient's blood and urine to a single oral dose of 1 gram was again determined. Table 3 shows a comparison of the response of the patient's excretion of vitamin C following the oral administration of 1 gram of the vitamin during the control period and after the administration of vitamin C. It will be observed that following the generally accepted ideas of saturation with the vitamin that the patients after therapy at a level of 200 mg. per day of the vitamin have become saturated.

These observations would indicate that the requirements of an arthritic individual for vitamin C were between 100 and 200 mg. per day or in other words between two and four times that of a normal individual.

Clinical Effects of Vitamin C in Rheumatoid Arthritis. None of the patients showed symptoms of the type associated with scurvy itself, in spite

TABLE III
Comparison of Amount of Cevitamic Acid Excreted in Urine Following an Oral Dose of 1000 mg. Before and After Cevitamic Acid Therapy in Patients with Rheumatoid Arthritis

Patient No.	Age	Sex	Control Period		Therapy			After Therapy		Per cent of Cevitamic Acid fed to the amount excreted
			Cevitamic Acid mg./100 c.c. blood serum	mg. Cevitamic Acid excreted in 48 hours	Per cent Cevitamic Acid fed to amount excreted in urine	mg. Cevitamic Acid per day	No. of Days	Cevitamic Acid mg./100 c.c. blood serum	mg. Cevitamic Acid excreted in 48 hours	
10	56	female	.320	15.76	1.58	100	11	1.300	252.64	25.26
16	47	female	.240	72.00	7.20	200	30	1.938	466.00	46.60
						100	11			
						200	12			
						300	8			
30	42	female	.700	145.00	14.50	300	16	1.230	460.00	46.00
32	23	male	.190	6.49	.65	100	11	1.24	523.66	52.37
						200	11			
38	51	female	.380	6.08	.61	100	11	1.43	356.42	35.64
						200	12			
41	61	female	.380	55.00	5.50	100	11	1.15	471.00	47.10
						200	12			
						300	8			
51	26	male	.190	18.00	1.80	100	11	1.33	178.20	17.82
						200	14			
52	41	male	.110	7.00	.70	100	11	1.03	515.52	51.55
						200	8			
56	17	male	.140	9.00	.90	100	11	.85	409.00	40.9
						200	15			
57	23	female	.310	6.43	.64	100	11	1.23	447.28	44.73
						200	8			

of the fact that many had cevitic acid levels below that usually present in this disease. In one case, there was a tendency to bleeding gums, but this did not clear up after the blood became saturated with vitamin C. Capillary fragility tests carried out by the method described by Wright and Lilienfeld¹³ (i.e. by counting the number of petechiae present in a uniform area on the forearm after 15 minutes of tourniquet pressure held at half-way between systolic and diastolic pressures) showed no significant increase when the plasma level of vitamin C was low, or decrease when the blood was saturated.

After eight months, during which time the patients were given vitamin C daily and their blood known to be saturated with vitamin C, no clinical improvement which could be attributed to the ingestion of vitamin C was observed. Some cases improved during this period, but others continued unchanged or became worse as judged by the condition of their joints, failure to gain weight or hemoglobin, and slowing of the red cell sedimentation rate.

No increase in the red blood cell count was found in any of the patients although occasionally sporadic but slight increases in the reticulocytes were observed.

This study indicates that the ordinary hospital diet was inadequate in its vitamin C content to supply the increased demands of the rheumatoid arthritic and may lead to a general revision of diets in institutions devoted to the care of this disease. Further investigation may discover additional deficiencies in the dietary requirements for other vitamins and essential nutritional substances.

SUMMARY

Seventy-five per cent of 56 cases of rheumatoid arthritis had a subnormal content of vitamin C in the blood. Fifty-nine per cent had levels below 0.5 mg. per 100 ml. These findings are confirmatory of those of Rinehart.^{9, 10}

Although some of the patients had had diets containing vitamin C well below the amount usually required for normal people, none of them presented clinical evidence of scurvy.

Patients with rheumatoid arthritis actually have a much greater demand for vitamin C than the normal individual. From a study of 10 patients with rheumatoid arthritis it was shown that these individuals could tolerate an intake of over 100 mg. and usually 200 mg. without marked excretion into the urine.

Following this investigation all patients with rheumatoid arthritis in the Hospital were placed on an intake of 200 mg. of vitamin C per day for 8 months. No improvement has been noted that could be attributed to the effect of the vitamin.

BIBLIOGRAPHY

1. ABT, A. F., FARMER, C. J., and EPSTEIN, I. M.: Normal cevitic (ascorbic acid) determinations in blood plasma and their relationship to capillary resistance, Jr. *Pediat.*, 1936, viii, 1.

2. VAN ECKELEN, M.: On the metabolism of ascorbic acid, *Acta brev. Neerland.*, 1935, v, 165.
3. HARRIS, L. J., and RAY, A. N.: Diagnosis of vitamin C subnutrition by urine analysis with a note on the antiscorbutic value of human milk, *Lancet*, 1935, i, 71.
4. YOUMAN, J. B., CORLETTE, M. B., AKEROYD, J. H., and FRANK, H.: Studies of vitamin C excretion and saturation, *Am. Jr. Med. Sci.*, 1936, cxc, 319.
5. VAN ECKELEN, M.: On the amount of ascorbic acid in the blood and urine. The daily human requirements for ascorbic acid, *Biochem. Jr.*, 1936, xxx, 1119.
6. HEINEMANN, M. I.: On the relation between diet and urinary output of thiosulphate and ascorbic acid, *Biochem. Jr.*, 1936, xxx, 2291.
7. FAULKNER, J. M., and TAYLOR, F. H. L.: Vitamin C and infection, *ANN. INT. MED.*, 1937, x, 1867.
8. FAULKNER, J. M., and TAYLOR, F. H. L.: Observations on the renal threshold for ascorbic acid in man, *Jr. Clin. Invest.*, 1938, xviii, 69.
9. RINEHART, J. F., GREENBERG, L. D., and BAKER, F.: Reduced ascorbic acid content of blood plasma in rheumatoid arthritis, *Proc. Soc. Exper. Biol. and Med.*, 1936, xxxv, 347.
10. RINEHART, J. F., GREENBERG, L. D., and CHRISTIE, A. U.: Reduced ascorbic acid content of blood plasma in rheumatic fever, *Proc. Soc. Exper. Biol. and Med.*, 1936, xxxv, 350.
11. FARMER, C. J., and AET, A. F.: Determination of reduced ascorbic acid in small amounts of blood, *Proc. Soc. Exper. Biol. and Med.*, 1936, xxxiv, 146.
12. TAYLOR, F. H. L., CHASE, D., and FAULKNER, J. M.: Estimation of reduced ascorbic acid in blood serum and plasma, *Biochem. Jr.*, 1936, xxx, 1119.
13. WRIGHT, IRVING S., and LILIENFELD, ALFRED: Pharmacologic and therapeutic properties of crystalline vitamin C (cevitamic acid). With special reference to its effects on the capillary fragility, *Arch. Int. Med.*, 1936, lvii, 241.

POSTOPERATIVE PROGRESSIVE EXOPHTHALMOS WITH LOW BASAL METABOLIC RATE *

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MORE than a century and a half has now elapsed since Parry,¹ in 1786, noted and described exophthalmos in the first classical case of exophthalmic goiter recorded in medical literature. Since then the problem of the etiology and pathogenesis of exophthalmos in association with thyroid disease has been the theme of numerous and intensive studies and investigations—clinical, pathologic and experimental. As the result of these studies, numerous theories of the pathogenesis of exophthalmos have been propounded (table 1), but a complete solution of the problem has not been reached. We have gained considerable knowledge when and how exophthalmos develops in thyroid disorders, but we do not know why it develops. Up to now, we have failed to penetrate into the mystery of the basic cause which is responsible for the pathologic changes which produce the exophthalmos.

We speak glibly of primary toxic goiter, or exophthalmic goiter, and secondary toxic goiter, or toxic adenomatous goiter, as forms of hyperthyroidism. Why, then, does exophthalmos occur very frequently in the primary type and very rarely in the secondary? Why does exophthalmos occur very frequently in mild or moderate cases of primary toxic goiter and very rarely in severe long standing cases of secondary toxic goiter? Why does exophthalmos recede in the majority of cases of exophthalmic goiter after successful thyroidectomy in the early stages of the disease and become severe and progressive in others? Why is exophthalmos absent in some very long standing severe cases of primary toxic goiter before operation, and why does progressive malignant exophthalmos first develop after a successful thyroidectomy with relief of general symptoms and a drop in basal metabolism to normal or minus rate? Regretfully, we have to admit that we have no satisfactory answer to these perplexing questions, for neither do we know the basic cause of toxic goiter nor of exophthalmos in association with goiter.

Nevertheless, despite our failure to discover the basic cause of exophthalmos in thyroid disorders, we have learned a number of facts about its course, pathogenesis and treatment which, if promptly and properly utilized, may be greatly helpful in its practical solution as a therapeutic problem.

POSTOPERATIVE PROGRESSIVE EXOPHTHALMOS WITH LOW BASAL METABOLIC RATE

1. *Frequency of Exophthalmos in Primary Toxic Diffuse Goiter and Its Rarity in Secondary Toxic Nodular Goiter.* The frequent occurrence

* Received for publication February 3, 1938.

From the Out-Patient Department, Beth Israel Hospital, New York City.

TABLE I
Theories of Pathogenesis of Exophthalmos in Graves' Disease

Year	Author	Theory of Pathogenesis	Basis for Theory
1834	Dalrymple ²	Spasm of levator palpebra superioris	The physiological function of the levator palpebra superioris "is to raise the upper lid, to uncover the globe of the eye by drawing the tarsal cartilage beneath the margin of the orbit, and at the same time it slightly protrudes the globe."
1840	Basedow ³	"Strumous" hypertrophy of retrobulbar cellular tissues	Increase of retrobulbar cellular tissues in a case of progressive exophthalmos with corneal ulceration and destruction of eye.
1849	Begbie ⁴	Increase of vitreous humor	Report of a prominent oculist who examined one of Dr. Begbie's patients and found "the sclerotics of both eyes were evidently distended from an increased secretion within."
1849	Cooper ⁵	Spasm of levator palpebra superioris; weakness and elongation of eye muscles; retrobulbar venous congestion	Clinical observations and studies.
1852	Bernard ⁶	Stimulation of cervical sympathetic	Electrical stimulation of cervical sympathetic in animals produced widening of palpebral fissures, dilatation of pupils and exophthalmos.
1853	Demarres ⁷	Hypertrophy of retro-orbital fatty tissue	Observation of one case of exophthalmic goiter with progressive exophthalmos, corneal ulceration and destruction of eye. When the eye was destroyed, "a terrible phlegmon" filled the orbital cavity.
1854	Stokes ⁸	Increase of aqueous and vitreous humor	Personal observation of the "clear, transparent and brilliant condition of the eyes free from any signs of 'sanguineous congestion' even in long standing marked exophthalmos." He had known of a case "in which for upwards of a year, the eye was never closed, yet in which no vascularity of the conjunctiva, nor any form of ophthalmia ever occurred."
1856	Taylor ⁹	Retro-orbital venous congestion secondary to impeded venous return from head and orbit	In two patients who died of exophthalmic goiter with signs of congestive heart failure, autopsy revealed dilatation of jugular veins.
1857	Graefe ¹⁰	Venous congestion leading to orbital edema and hypertrophy of fatty tissue	Dilatation of orbital veins on ophthalmoscopic examination; increase of retro-orbital fat found at autopsy.
1857	Egeberg ¹¹	Degeneration, weakness and elongation of eye muscles	Fatty degeneration and elongation of eye muscles found at autopsy in one case of exophthalmic goiter.
1857	Hervieux ¹²	Dilatation and turgescence of orbital arteries	Hyperactivity of heart and marked pulsation of peripheral arteries in exophthalmic goiter.
1860	Aran ¹³	Irritation of cervical sympathetic causing contraction of Muller's muscles of orbit	Claude Bernard's demonstration in 1852 that stimulation of the cervical sympathetic in dogs causes exophthalmos; Muller's discovery of smooth muscles in orbit.

TABLE I—*Continued*

Year	Author	Theory of Pathogenesis	Basis for Theory
1864	Laycock ¹⁴	Irritation of cervical sympathetic causing contraction of Muller's muscles of orbit	Claude Bernard's experimental production of exophthalmos by stimulation of first and second dorsal nerve roots; and presence of neuralgic pains along distribution of seventh and eighth cervical and first and second dorsal nerve roots in two cases of exophthalmic goiter observed by Laycock.
1867	Traube and Recklinghausen ¹⁵	Increase of retrobulbar fat and degeneration of extra-ocular muscles	Autopsy findings in a case of exophthalmic goiter.
1878	Filehne ¹⁶	Brain irritation	Section of restiform bodies in animals resulted in exophthalmos.
1886	Jackson ¹⁷	Brain irritation	Claude Bernard's and Filehne's experimental production of exophthalmos by section of restiform bodies.
1886	Bristow ¹⁸	Increase of orbital fat	Autopsy findings in three fatal cases of exophthalmic goiter.
1894	Buschan ¹⁹	Excessive filling of orbital vessels	Compressibility of bulb; fluctuation of exophthalmos; partial or complete subsidence of exophthalmos after death; pulsation of retinal vessels on ophthalmoscopic examination; sudden appearance of exophthalmos in some patients; production of exophthalmos in rabbits by ligation of jugulars.
1896	Jaboulay ²⁰	Stimulation of cervical sympathetic	Resection of cervical sympathetic in two cases of Graves' disease was followed by recession of exophthalmos.
1897	Reclus and Faure ²¹	Stimulation of cervical sympathetic	For 10 years a patient with marked exophthalmos of Graves' disease could not sleep with closed eyes. Following bilateral resection of cervical sympathetic the exophthalmos receded within 24 hours and the patient was able to sleep with closed eyes.
1900	Edmunds ²²	Hyperthyroidism	Experimental production of exophthalmos in monkeys and rabbits by thyroid feeding.
1907	Landstrom ²³	Stimulation of Landstrom muscle by sympathetic	Rudimentary development of Muller's muscle in man; Landstrom's discovery of smooth muscle between the equator of the bulb and the upper and lower lids.
1907	Birch-Hirschfeld ²⁴	Stasis of retro-orbital lymphatic vessels	Paraphenyldiamin hydrochloride injections in dogs, rabbits and monkeys produced exophthalmos. Histological studies revealed dilatation of lymph sinuses of orbit.
1912	Fründ ²⁵	Spasmodic contraction of smooth muscle surrounding ophthalmic veins	Anatomic dissection of the eyes in newborn showed smooth muscle surrounding small and large ophthalmic veins.
1912	Sattler ²⁶	Brawny edema of retro-orbital tissues	Contraction of Muller's and Landstrom's muscles inadequate to cause exophthalmos. Brawny edema akin to brawny edema met with elsewhere in the body in Graves' disease is most probable cause of exophthalmos.

TABLE I—*Continued*

Year	Author	Theory of Pathogenesis	Basis for Theory
1916	Troell ²⁷	Orbital edema?	Experiments with paraphenyldiamin hydrochloride in dogs produced orbital edema and exophthalmos even when the cervical sympathetic was extirpated. Stimulation of sympathetic failed to substantiate observations of MacCallum and Cornell and Cannon.
1917	Wilson ²⁸	Weakness and relaxation of extra-ocular muscles	In eight autopsied cases of exophthalmic goiter very little fat and very little venous engorgement were found. The extra-ocular muscles were small and degenerated. Hence he assumed relaxation of the recti muscles as the cause of the exophthalmos.
1920	Moore ²⁹	Excess fat, orbital edema and hypertrophy of the extra-ocular muscles	Findings in two cases. Postmortem dissection of the orbit in one case revealed "that after death the exophthalmos was marked and was only as much less than during life as might be accounted for by the draining of blood from the orbit after death. . . . It is clear that in this particular case neither sympathetic irritation nor blood engorgement was the cause of the proptosis. It is difficult to identify what is an excess fat in a cavity which is normally full of it. In this case, however, the orbit was certainly full of it to overflowing with it and nothing else." In the second case exploration of the orbital cavity revealed excess fat. "In addition, however, the fat seemed edematous, and in particular the inferior, internal and external recti muscles were exposed for a considerable distance and these, instead of being thin, flat, ribbon-like muscles, such as one becomes familiar with in squint operations, were greatly swollen fusiform bellies apparently from edematous infiltration, not quite as stout as the joint of one's little finger."
1921	Whitnall ³⁰	Dilatation of the orbital vessels by excitation of the sympathetic nervous system	"The exophthalmos is said to disappear after death, and in a dissection of two orbits taken from a subject who had died from the disease and had presented the well-marked signs, nothing abnormal could be found by the writer."
1921	Plummer ³¹	Dysthyroidism due to action of abnormal thyroxin	In pure hyperthyroidism, clinically encountered in toxic adenomatous goiter, exophthalmos is rarely present. "The characteristics of exophthalmic goiter may be due to an incomplete thyroxin molecule."
1927	Kunde ³²	Hyperthyroidism	Experimental production of exophthalmos in rabbits by administration of thyroid.
1931	Labbe ³³	Thyro-sympathetic hyperactivity	Experimental production of exophthalmos in animals and man by synergetic action of thyroxin and sympathomimetic drugs; recession of exophthalmos under yohimbin therapy.

TABLE I—*Continued*

Year	Author	Theory of Pathogenesis	Basis for Theory
1931	Gasteiger ³⁴	Localized myxedema of orbital tissues	Observation of one case of postoperative progressive exophthalmos with marked orbital edema and low basal metabolic rate cured by thyroid feeding.
1931	Stewens ³⁵	Localized myxedema of orbital tissues	Presence of non-pitting edema of orbital tissues in a case of postoperative progressive exophthalmos with low basal metabolic rate. Biopsy of chemotic tissue showed edema and round cell infiltration similar to that found in localized myxedema described by Richter and O'Leary.
1931	Loeb ³⁶	Hyperpituitarism causing secondary hyperthyroidism	Experimental production of exophthalmos and other signs of Graves' disease by administration of thyrotropic hormone of pituitary to animals.
1932	Crile ³⁷	Hypothyroidism following operation for hyperthyroidism	Clinical observation of progressive exophthalmos with low basal metabolic rate following operation for hyperthyroidism.
1932-1934	Marine ^{38, 39, 40}	Hypothalamic stimulation by metabolic disturbances of non-endocrine and endocrine origin	Experimental production of thyroid hyperplasia and exophthalmos by methyl cyanide injections in rabbits; production of exophthalmos by thyrotropic hormone of pituitary; increase of exophthalmos, after thyroidectomy, under continued administration of methyl cyanide and thyrotropic hormone; abolition of exophthalmos by section of cervical sympathetic.
1932-1933	Naffziger ^{41, 42, 43}	Tremendous hypertrophy of extra-ocular muscles with round cell infiltration of muscles and retro-orbital tissues.	Findings at operation for postoperative progressive exophthalmos with low basal metabolic rate.
1933	Urechia ⁴⁴	Thyro-sympathetic hyperactivity	Experimental production of exophthalmos of Graves' disease by injections of thyroxin and ephectonine.
1934	Viallefont and Lafon ⁴⁵	Mid-brain irritation	Ocular signs of Graves' disease occur in diseases of the midbrain in the absence of Graves' disease; increase of iodine in midbrain and cerebrospinal fluid in Graves' disease.
1934	Zalka ⁴⁶	Inflammatory reaction of orbital tissues	Findings at autopsy in 11 out of 16 cases of Basedow's disease.
1934	Drouet ⁴⁷	Primary hyperpituitarism, secondary hyperthyroidism	Clinical and laboratory evidence of hyperactivity of pituitary in Graves' disease; cure of Graves' disease by primary irradiation of pituitary.
1935	Borak ⁴⁸	Hyperpituitarism and hyperthyroidism	Cure of cases of Graves' disease including recession of exophthalmos by irradiation of pituitary in patients who were refractory to thyroid radiation.
1936	Thomas and Woods ⁴⁹	Chronic inflammatory reaction of orbital tissues	Pathologic findings at operation and autopsy.
1936	Smesler ⁵⁰	Inflammatory reaction of orbital tissues secondary to hyperpituitarism	Experimental production of extreme exophthalmos in thyroidectomized and sympathectomized animals by administration of thyrotropic hormone of pituitary; presence of inflammatory reaction in orbital tissues.

of exophthalmos in primary toxic goiter and its great rarity in secondary toxic goiter, is a common observation. In the experience of different observers, the incidence of exophthalmos in primary toxic goiter varies from



FIG. 1 (Case 1). Postoperative persistent exophthalmos with low basal metabolic rate and myxedema following thyroidectomy and right sympathectomy for Graves' disease. 1925—one year after operation.

50 to 80 per cent, increasing in frequency with the duration of the disease. The degree of protrusion bears no strict relation to the severity of the other clinical manifestations of the disease. Occasionally exophthalmos may be present not only as the first but apparently as the only symptom of Graves' disease. It may then be mistaken for exophthalmos of non-Graves' origin. Its serious import and grave potentiality may then be entirely overlooked, with serious results to the patient. Such an experience at Johns Hopkins Hospital was recently recorded by Friedenwald.⁵¹

"A patient came to the hospital in 1924 with a history that three months before he had had an acute infection of the upper respiratory tract, rhinitis and fever,

followed a week later by coma and convulsions, which lasted for a week. Three months after the onset he came to the Eye Dispensary, and was found to have moderate exophthalmos of the right eye, with limited movement of the eyeball, a beginning corneal ulcer and the appearance of an orbital abscess. There was no

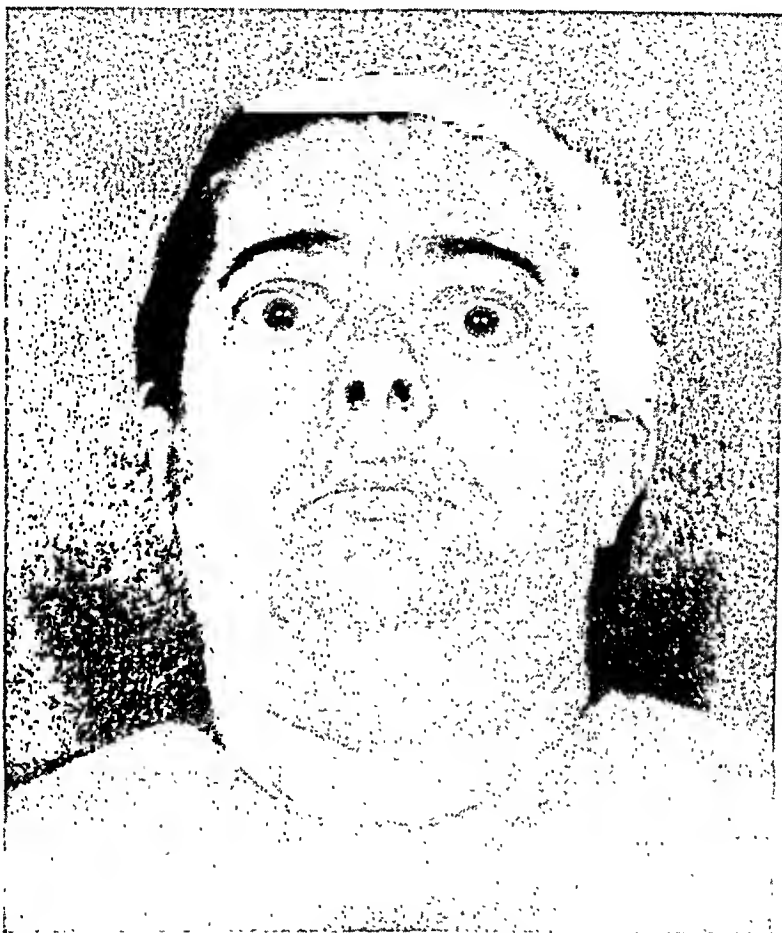


FIG. 2. Same patient as in figure 1. Persistent exophthalmos under thyroid medication. 1932—eight years after operation.

enlargement of the thyroid at that time, and there was no increase in pulse rate. A basal metabolism was not made, but attention was concentrated on the possibility of sinusitis and an orbital abscess. The patient returned three months later, having suffered a great loss of weight. His thyroid was palpable; there was bilateral exophthalmos and papilledema, and the pulse rate was much increased. A diagnosis of acute hyperthyroidism was quite obvious, and the ocular condition was thought to be a possible complication—an abscess of the brain or an orbital abscess. The patient became delirious, bilateral acute glaucoma developed, and he finally died. At autopsy, the orbits were carefully explored on account of the suspicion of an orbital abscess, but no abscess was found, and no note was made of any enlargement. The extra-ocular muscles were preserved, and the specimen was sent to the laboratory. Study showed changes identical with those shown in the cases presented by Dr. Naffziger (table 1)."

2. *Rarity of Serious Eye Complications in the Average Case of Exophthalmic Goiter.* In the mild or average case of exophthalmos in Graves'

disease, no serious eye complications have been encountered. The proptosis may be disfiguring and an annoying symptom but does not constitute a serious clinical problem. As pointed out originally by Stokes and cor-



FIG. 3. Same patient as in figure 1. Postoperative persistent exophthalmos with low basal metabolism partially relieved by thyroid medication. 1938—13 years after operation.

roborated by many observers, marked exophthalmos with inability to keep the eyes closed at night may exist for a year or longer without any evidence of conjunctival congestion or impairment of vision. We have observed a patient with postoperative exophthalmos and myxedema over a period of 13 years (figures 1, 2, 3). At times the proptosis was so marked as to result in subluxation of the globes and yet up to now no impairment of vision has been demonstrated on repeated ophthalmological examination. The latest examination made a few months ago showed no contraction of visual or color fields. However, one must not overlook the fact that exophthalmos

in Graves' disease is always a source of potential danger and should always receive prompt medical attention and careful supervision and treatment. One can never tell when an exophthalmos, apparently stationary for many months, may suddenly become progressive and malignant and result in corneal ulceration and destruction of the eye. Such was a recent experience in a patient with exophthalmic goiter whose exophthalmos was stationary



FIG. 4 (Case 2). Marked bilateral exophthalmos in a case of severe Graves' disease. Exophthalmos stationary for a period of eight months.

for many months without any ocular complications. Then, suddenly, after thyroidectomy, within a period of two weeks she developed acute progressive exophthalmos with corneal ulceration and destruction of the left eye which required evisceration (figures 4 and 5).

The danger of delay in the treatment of progressive exophthalmos in Graves' disease was recently stressed by Naffziger in his excellent review of the entire problem: In marked or severe exophthalmos occur muscle palsies, retinitis, optic atrophy, corneal congestion, chemosis, corneal ulcera-

tion, panophthalmitis with loss of both eyes followed at times by meningitis and death.

3. *Recession of Exophthalmos in Graves' Disease after Successful Treatment by Medical or Surgical Measures or Radium and Roentgen Therapy.* In the majority of cases of exophthalmic goiter, following successful treatment by medical, surgical or irradiation therapy, the exoph-



FIG. 5. Same patient as in figure 4. Postoperative progressive exophthalmos with destruction of left eye within a period of two weeks following thyroidectomy and continued use of Lugol's solution.

thalmos recedes completely or partially, or remains stationary, depending upon the duration and the mechanism of production of the proptosis. Evidently one cannot expect the recession of exophthalmos in those long standing cases in which there has taken place marked increase of the retro-orbital cellular tissues with hypertrophy or atrophy and degeneration of the extra-ocular muscles. However, every experienced observer has been im-

pressed by the frequent recession of early exophthalmos when the thyrotoxic symptoms have been controlled and the basal metabolism has been brought down to normal or subnormal rates.

4. *Postoperative Progressive Exophthalmos With Low Basal Metabolic Rate.* Unfortunately, not always does exophthalmos recede after a successful surgical operation for exophthalmic goiter. What is most remarkable—greatly illuminating or puzzling, according to one's theory of the nature of Graves' disease—such cases have been observed after thyroidectomy with sufficient removal of thyroid tissue to produce a normal or minus basal metabolic rate (table 2). In the words of Naffziger, the usual development of the condition is as follows:

TABLE II
Postoperative Progressive Exophthalmos With Low Basal Metabolic Rate

Year	Author	No. of Cases	BMR	Treatment	Result
1925	Plummer ³¹	1	-14	Iodine and thyroid.	Improved.
1929	Zimmermann ⁵²	11	-15 to -19	Iodine and thyroid.	Unimproved.
1929	Benedict ⁵³	6	Normal	Type of treatment not stated.	"The exophthalmos increased with ecchymosis of the conjunctiva and swelling of the lid and one or both eyes were lost."
1929	Burch ⁵⁴	1	.	Thyroid, iodine, roentgen-ray therapy to orbit.	No improvement. Loss of both eyes.
1930	Roeder and Killins ⁵⁵	4	-12 to -21	Thyroid and iodine.	No improvement in any case, aggravation of general symptoms in one case.
1931	King ⁵⁶	5	-10 to -19 in 3, normal in 2.	Thyroid and iodine.	Thyroid medication was followed by increase of exophthalmos, iodine gave temporary improvement with relapse.
1931	Earnest and Serger ⁵⁷	1	-4	Iodine.	Slight improvement.
1931	Gasteiger ³⁴	1	Not stated. Myxedematous swelling of eyelids.	Thyroid.	Cured.
1931	Stewens ⁵⁸	1	Not stated	Thyroid, roentgen-ray therapy, hypophysis and pituitrin injections.	Thyroid feeding aggravated exophthalmos; roentgen-ray therapy relieved pain but caused no recession; marked improvement after hypophysis and pituitrin injections.
1931	Naffziger ⁴¹	1	-32	Naffziger decompression operation.	Marked improvement.
1932	Naffziger ⁴²	7	Minus BMR	Naffziger decompression operation.	Marked improvement.
1932	Semmer ⁵⁸	1	-13	Naffziger operation.	Marked improvement.

TABLE II—*Continued*

Year	Author	No. of Cases	BMR	Treatment	Result
1933	Merrill and Oakes ⁵⁹	2	Minus BMR	Scarification of edematous conjunctiva, multiple punctures, canthoplasty, conjunctivoplasty, resection of redundant welts of conjunctiva, suturing of lids, roentgen-ray therapy to orbit.	No improvement. Corneal ulceration and loss of both eyes.
1934	Cattell ⁶⁰	12	Normal	Not stated in 10; Naffziger operation in two.	Not stated.
1934	Bothman ⁶¹	4	-9 to -16 in two; not stated in two.	Iodine, sympathectomy, removal of roof of orbit, Naffziger operation, tarsorrhaphy.	Lugol's solution, bilateral sympathectomy, removal of roof of orbit ineffectual; Naffziger operation gave moderate improvement in one; tarsorrhaphy in another.
1934	Goldenberg ⁶²	1	-17.8	Canthotomy, later. Naffziger operation.	Improvement after Naffziger operation.
1934	Nordland and Larsen ⁶³	2	-19 and -32	Not stated.	Progressive exophthalmos.
1934	Brisay ⁶⁴	3	plus 8 to minus 23	Iodine, thyroid, eserine salicylate, ergotamine tartrate, excision of a piece of conjunctival sac, tarsorrhaphy.	Improvement in two cases; result not stated in one case.
1936	Rynearson ⁶⁵	2	-4 to -14	Iodine and thyroid.	Improved and relapsed despite prolonged treatment in one case; result "to be noted in the other."
1936	Thomas and Woods ⁴⁹	14	Normal in 12; myxedema in two with BMR -30 in one and plus 35 in the other.	Thyroid in five cases; iodine in two; tarsorrhaphy in three; roentgen-ray therapy to orbit in one.	No improvement. No improvement. Not stated. Improved.
1937	Rudemann ⁶⁶	4	Not stated, myxedema of orbit present.	Roentgen-ray therapy.	"In none of them is the exophthalmos progressing as before."

"Thyroidectomy is performed on a patient with exophthalmic goiter who presents the usual elevated basal metabolic rate and cardiovascular and nervous manifestations. Clinical improvement follows, except that the exophthalmos does not disappear. In a variable period, often in three or four months, it becomes evident that the proptosis is increasing. As it proceeds an increased fullness of the lids is noted; then lacrimation and epiphora appear. A watery appearance of the scleral conjunctiva is followed first by edema near the inner canthus and then by swelling, which spreads rapidly, and protrusion of the inferior palpebral mucosa. Diplopia and lack of parallelism of the eyes are followed by an increasing limitation of the movements of the globe, and downward movements are the only ones retained ultimately. In other directions there may be only slight movement. During the increasing protrusion of the eyes through these stages the lids no longer completely cover the globe, and the cornea

becomes exposed. Such patients are said to be suffering from malignant exophthalmos, for while cases of less severity may be seen, the severe cases invariably have progressed to the stage of corneal ulceration and infection. Many enucleations have been performed, but the usual termination has been an infected orbit, intracranial extension of the infection and death."

5. *Treatment of Postoperative Progressive Exophthalmos With Low Basal Metabolic Rate.* The treatment of severe cases of postoperative progressive exophthalmos with low basal metabolic rate by the usual methods of sympathectomy, tarsorrhaphy, canthotomy, corneal scarification and local eye applications have not been satisfactory (table 2). In many of these cases, despite such treatment, ulceration of the cornea and destruction of the eyes could not be averted. In some, even if the eyes were saved, marked impairment of vision from keratitis, retinitis, or optic atrophy, resulted. The dread and hopelessness with which this condition was looked upon by the profession can best be visualized by citing the following quotation from a recent publication of an experienced thyroid surgeon.

"A man, aged 36, consulted me in 1928, with an acute and very active exophthalmic goiter. He was operated upon, made an excellent recovery, gained weight, and felt fine for a period of four months, when his father became ill and he was called East to be with him through a long and distressing illness, resulting in death. My patient returned to Seattle in April, 1930, with evidence of recurrence of his goiter. In addition to the usual symptoms of moderate severity, he then had a slight degree of bilateral exophthalmos. He was reoperated on in the latter part of April, again making a good recovery. All symptoms of goiter, except exophthalmos, soon disappeared. The condition of his eyes rapidly became worse—the prominence accentuated, the edema more pronounced, the difficulty with vision increased to a point at which he is unable to work. Twice during recent months, the vessels surrounding the cornea have become injected similar to the condition seen in association with corneal ulcer though no ulcer has as yet developed. I feel that if an ulcer develops in this man's cornea, the probability of blindness following it is very great. . . . As yet no satisfactory treatment has been devised for this most distressing condition."

Hardly had Dr. King pronounced this gloomy prognostication when one of the most dramatic announcements—with which medical history is so replete—was made by Dr. Naffziger of San Francisco, who attended the meeting at which Dr. King read his paper on "The Cause of Exophthalmos" in Graves' disease.

"A nurse," Dr. Naffziger began, "had, following thyroidectomy, a rapidly increasing exophthalmos with a low (minus 32) basal metabolic rate. Her vision had become so impaired that she could not recognize people at five feet. This was due to a papillitis associated from some atrophy. In view of her desperate condition, it seemed justifiable to explore the orbit and decompress it. This was done through a frontal flap exposing the orbit from above. The orbital plate was then removed on the right side. The contents appeared very tense and bulged through the decompression. The tissues appeared somewhat edematous. The fat did not appear to be increased, nor was it under tension. The cone of extra-ocular muscles was tense, but the striking feature was their great thickness. The muscle fibers were separated in the line of their direction. They did not cut like normal musculature. The question then arose as to why the choked disc existed. It appeared possible that

the nerve might be compressed at the foramen. The optic nerve was exposed through the musculature and appeared normal. In order to free the optic nerve posteriorly bone was removed from the optic foramen and the ring of Zinn was opened, actually decompressing the optic nerve itself. Following operation, there was reduction by the exophthalmometer from 34 to 23, which subsequently came up to 27, but never exceeded that level. From the fifth day the vision was markedly improved. The patient was able to read with that eye shortly after. She was so pleased with the result that about three weeks later she returned with a request that the other eye be operated upon. This was done with the same pathological findings and with the same results. The microscopic picture of the muscle is one of marked fibrosis, round cell infiltration and hyaline changes."

One year later Naffziger was able to report on five more patients in whom the clinical course and operative findings paralleled those of his first case. The results of the decompression operation were uniformly successful.

"In each instance there was early improvement in vision, subsidence of the papillitis and disappearance of the hemorrhage. The recession of the globes continued over many months and varied from 2 to 7 degrees on the exophthalmometer. In no case has there been any tendency to recurrence. In each instance the globes show faint pulsation of which the patient is unaware."

MEDICAL TREATMENT OF POSTOPERATIVE PROGRESSIVE EXOPHTHALMOS WITH LOW BASAL METABOLIC RATE

While the beneficial results of the Naffziger operation have been confirmed by a few other surgeons, the operation is a formidable one. The amount of recession of the exophthalmos is only moderate in degree. Although the pulsation of the globe in the cases personally operated upon by Dr. Naffziger has been only faint, we have been informed of one case done by a neuro-surgeon where the pulsation was sufficiently marked to make the patient disagreeably conscious of its presence. Moreover, the rationale of the procedure is mechanical relief: the Naffziger decompression operation does not remove the underlying basic cause of the pathologic process. Hence in the milder grades and in the earlier stages of progressive exophthalmos medical treatment has its place and has been carried out by a number of clinicians.

The first to report on the successful medical treatment of a case of post-operative progressive exophthalmos with low basal metabolic rate was Dr. Henry S. Plummer from the Mayo Clinic in 1925. Before operation for exophthalmic goiter the patient had shown a basal metabolic rate above plus 80

"and since operation a rate of -14, characteristic nervous phenomena and progressive exophthalmos. When this patient is placed on Lugol's solution, the nervous phenomena disappear, the exophthalmos recedes, the basal metabolism drops to -28, and edema, slow speech, and so forth, the characteristics of myxedema, appear within two weeks. When iodine is administered and the basal metabolism is maintained at the average normal with thyroxin, there is no evidence of disease except slight

exophthalmos. Many similar cases have been observed. . . . I have seen the complex that terminates in panophthalmitis and loss of the eyes progress rapidly almost to the point of forcing enucleation, stop and begin to recede within five hours after 100 minims of Lugol's solution had been given."

Unfortunately, Plummer's favorable results in postoperative progressive exophthalmos with low basal metabolic rate by means of iodine and thyroid treatment were very rarely obtained by other observers (table 2). Thus in 11 cases reported by Zimmermann no benefit was obtained from the combined use of iodine and thyroid. In one case, reported by Burch, iodine and thyroid failed to produce any improvement and the patient lost both eyes. In four cases observed by Roeder and Killian, thyroid and iodine produced improvement in no case and aggravation of symptoms in one. In King's five patients iodine medication gave temporary improvement with relapse, while administration of thyroid was followed by increase of exophthalmos. A cure in one case was reported by Gasteiger, but his patient presented frank myxedema of the orbits. Stewens, Naffziger, Semer, Merrill and Oakes, Cattell, Bothman, Rynearson, Thomas and Woods failed to obtain any benefit from iodine and thyroid medication. Favorable results in one case were claimed by Stewens from the use of hypophysin and pituitrin injections and in two cases by Brisay from the combined use of iodine, thyroid, eserine salicylate, ergotamine tartrate plus excision of a portion of the conjunctival sac and tarsorrhaphy. In short, with few exceptions, medical therapy has been rather disappointing in severe forms of postoperative progressive exophthalmos with low basal metabolic rate.

RADIOTHERAPY TO ORBITAL AND PITUITARY REGIONS IN POSTOPERATIVE PROGRESSIVE EXOPHTHALMOS WITH LOW BASAL METABOLIC RATE

The first to mention the use of roentgen therapy for the treatment of postoperative progressive exophthalmos was Burch in 1929. After iodine and thyroid had failed to produce any benefit the malignant clinical course of the exophthalmos suggested the diagnosis of sarcoma of the orbit. Intensive irradiation was used. There was no improvement and the patient lost both eyes from corneal ulceration and destruction. Burch gives no details as to the technic of the roentgen-ray therapy used in his case. In view of the diagnosis of sarcoma of the orbit, it is fair to assume that very large doses of roentgen-rays were used, with probable deleterious result. While large doses of roentgen-rays are frequently helpful, at least temporarily, in malignant growths, they are usually harmful in inflammatory and degenerative processes. Hence the failure of roentgen-ray therapy in this case is no criterion of the value of proper irradiation of the orbit in postoperative progressive exophthalmos, in which condition the most constant pathologic findings are those of inflammation of the orbital cellular tissues and hypertrophy or atrophy and degeneration of the extra-ocular muscles. In the next case, reported by Stewens in 1931, pain in the eye was relieved promptly but recession of exophthalmos was not obtained after

the use of a small dose of roentgen therapy. Nor were Merrill and Oakes more fortunate in their results. Definite improvement from orbital irradiation was first reported by Thomas and Woods in 1936 in one case and by Rudemann in 1937 in four cases. In a case recently observed in the Out-Patient Department of Beth Israel Hospital, the prolonged use of iodine and thyroid was a complete failure while roentgen-ray therapy to the orbital and pituitary regions was of distinct benefit.

CASE REPORT

In the early part of October 1935, without any apparent predisposing or exciting causes, M. E., aged 51 years, became nervous, irritable and shaky. Not until six months later did he notice slight protrusion of his eyes. Although he retained his strength and was able to carry on his usual work as pressor of cloaks, the staring and terror-stricken expression of his eyes and his trembling hands made his employer regard him distrustfully and make disparaging remarks about his "crazy" looks and

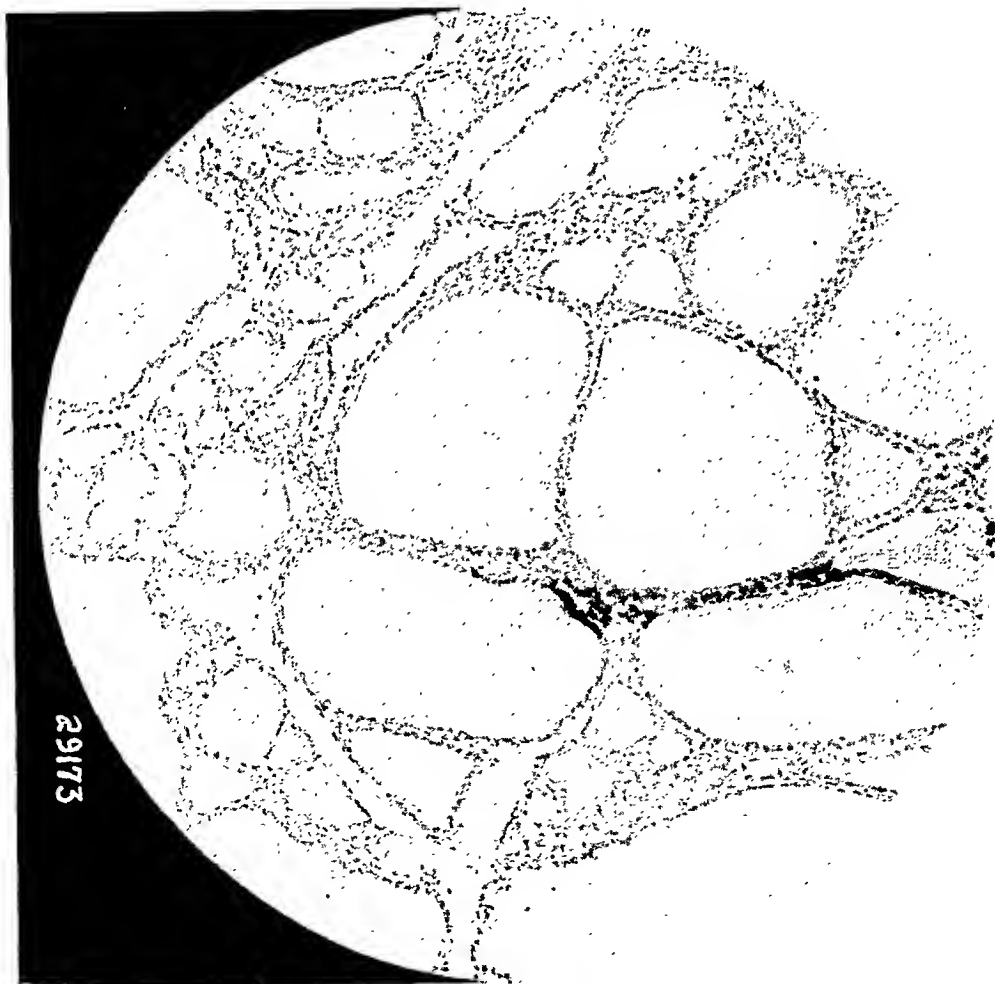


FIG. 6 (Case 3). Microphotograph showing moderate thyroid involution following the preoperative use of 360 minims of Lugol's solution.

shaking hands. Humiliated and unnerved by these remarks, he left this place to look for employment in a more friendly environment. He was successful in this quest, but the change failed to produce any improvement in his condition. His irritability and nervousness grew more marked. He had unaccountable and uncontrollable outbursts of temper which greatly distressed and puzzled him. It was for this change in temperament that he first consulted a physician in May 1936, seven months after the onset of his first complaints.

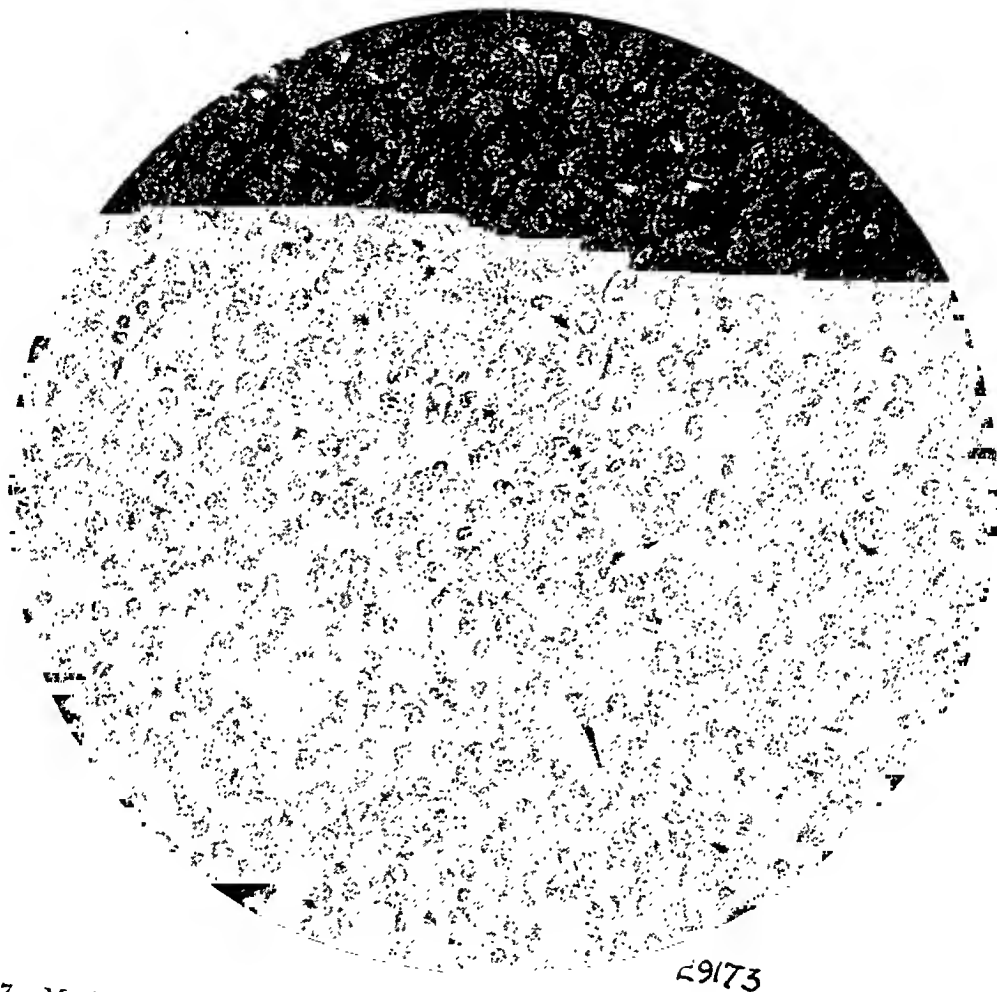


Fig. 7. Marked thyroid hyperplasia and hypertrophy. Microphotograph of a different field from same section of excised thyroid in case 3. Compare with figures 6, 8 and 9.

The examination failed to elicit any thyroid enlargement, but the other signs of exophthalmic goiter were unmistakable and a basal metabolism was suggested. He refused to take the test because he "still felt too well" to undergo a special examination for which a fee had to be paid. He was given sedative medication but his irritability and emotional outbursts gradually increased. He lost weight and strength progressively. The exophthalmos became more marked. Strangely enough, despite all the classical signs of Graves' disease, he had no heat intolerance but the reverse. During the months of July and August he frequently felt chilly and his hands would get blanched and "dead-like."

Towards the end of August 1936, his general condition had greatly deteriorated and his loss of weight amounted to 20 pounds. He felt very weak and shaky and was forced to give up his work. He felt greatly depressed and cried frequently under slight or no provocation.

In September, 1936, he was admitted to the Surgical Service of Beth Israel Hospital. On examination he showed all the classical signs of exophthalmic goiter

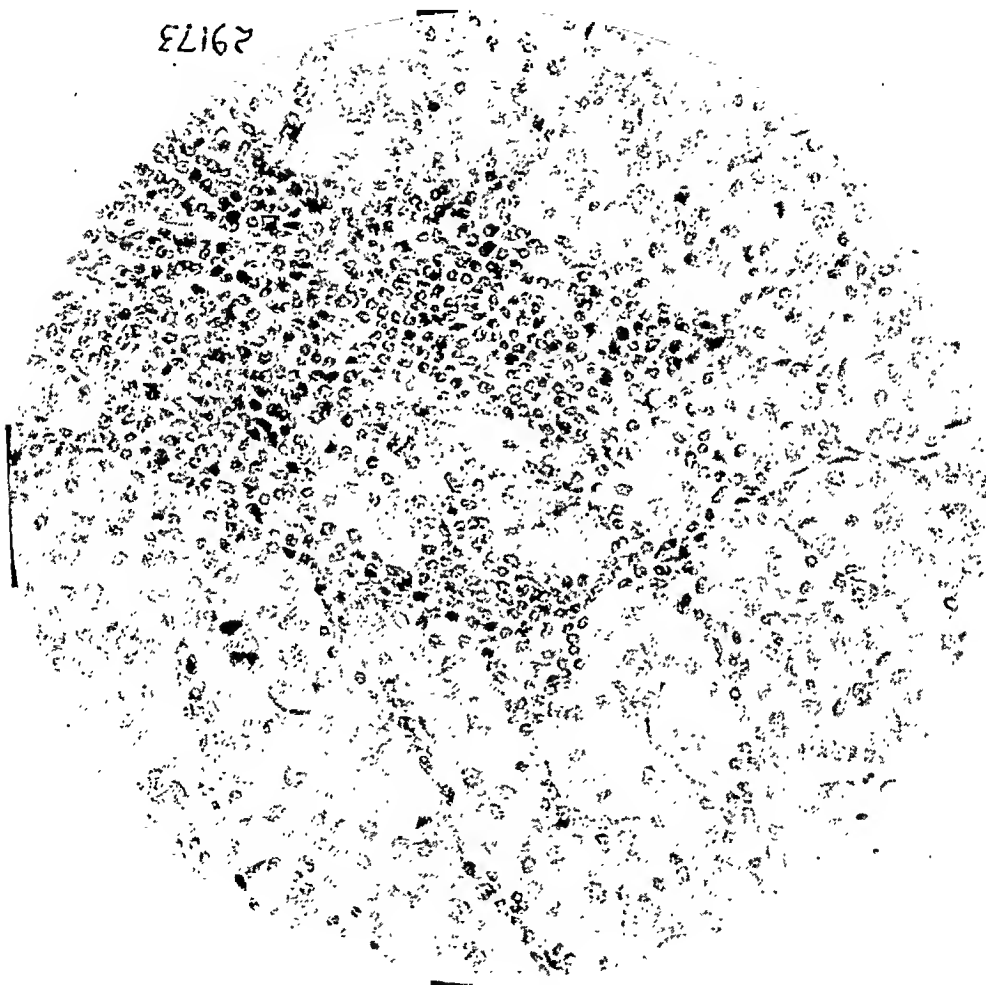


FIG. 8. Marked thyroid hyperplasia, hypertrophy and round cell infiltration. Microphotograph of another field from the same section of excised thyroid in case 3. Compare with figures 6, 7 and 9.

with marked exophthalmos and slight thyroid enlargement. The basal metabolism was plus 25. Physical and radiographic examination of the heart and lungs was negative. Blood and urine analyses were practically normal.

A diagnosis of uncomplicated exophthalmic goiter was made and thyroidectomy decided upon.

Following the use of 360 minims of Lugol's solution over a period of 15 days, the basal metabolism dropped to plus 12 and on October 10, 1936, a subtotal thyroidectomy was performed under general anesthesia by Dr. I. Busch. A study of the

excised thyroid tissue revealed marked iodine involution of the greater part of the microscopic field with many discrete areas of persistent glandular hypertrophy and hyperplasia, round cell infiltration and lymphoid hyperplasia (figures 6, 7, 8, 9).

The postoperative course was uneventful but the use of Lugol's solution was continued 5 minims three times daily. On October 21, 1936, 11 days after operation, the wound was healed, the patient's general condition was greatly improved and

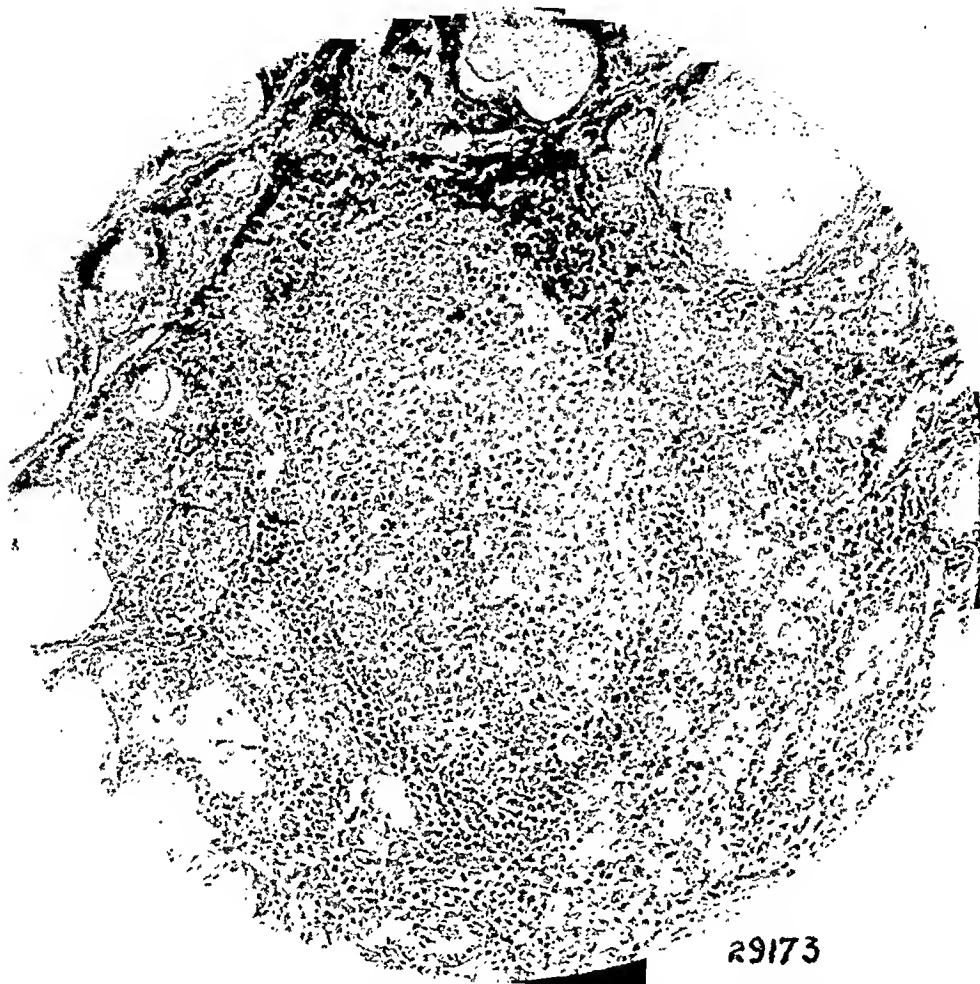


FIG. 9. Moderate thyroid hypertrophy and marked lymphoid hyperplasia. Microphotograph of another field from the same section of excised thyroid in case 3. Compare with figures 6, 7 and 8.

the basal metabolism had dropped to minus 11. He was discharged from the hospital and was advised to continue the use of Lugol's solution. Nevertheless, despite the continued use of iodine the exophthalmos did not recede, and one week later was definitely on the increase. He was then promptly referred for treatment to the out-patient eye clinic. On November 15, 1936, he was examined by Dr. Slomka of the ophthalmological department who found bilateral exophthalmos and all other ocular signs of Graves' disease. There was no lagophthalmos. The lids closed completely. The conjunctivae were congested but the media were clear. The fundi showed slightly pale optic discs. The retinal vessels were thin but otherwise normal.

Under continued use of Lugol's solution and local eye treatment there was no improvement. On November 30, 1936, the exophthalmos had noticeably increased. The protrusion of the left eye was 22 mm., that of the right 27 mm. The right conjunctiva was congested. The cornea and media were clear. The left fundus showed



FIG. 10 (Case 3). Postoperative progressive exophthalmos with low basal metabolic rate three months after operation and continued use of Lugol's solution.

no abnormality, the right showed slight venous congestion. For the next six weeks, despite the continued use of Lugol's solution and local eye medication, the eyes failed to improve (figure 10). A basal metabolism test on January 19, 1937, showed 18 per cent minus. He was then placed on desiccated thyroid grain 1 three times daily, increased later to grains 2 three times daily. There was no improvement. On April 20, 1937, the basal metabolism had risen to plus 13. His pulse showed moderate acceleration and he had slight tremor of fingers but the eyes were much worse. Exophthalmometric readings showed protrusion of the left 22.5 mm., that of the right 30 mm. The right conjunctiva was markedly congested and chemotic. The fundi were normal and there was no contraction of the visual fields. For the next three weeks local treatment of the eye and the internal use of Lugol's

solution and desiccated thyroid were continued without any improvement. At this time the chemosis and congestion of the right conjunctiva were very marked and diplopia developed due to paresis of the superior and external right rectus muscles (figure 11). The marked progression of the exophthalmos in the right eye and the apparently stationary condition in the left raised the question of a possible orbital



FIG. 11. Same case as in figure 10, showing progression of exophthalmos despite prolonged use of iodine and thyroid (May 24, 1937).

neoplasm and a roentgen-ray study of the orbit was made. The radiologist's report on May 12, 1937, stated: "The cranial cavity is of normal size. The cranial vault is of normal thickness. There is no increase in intracranial pressure. There is no abnormal intracranial calcification. The sella turcica is normal in size, shape and position and shows no lesion or destruction. There is no calcification of the petroclinoid ligament or inter-clinoid ligament. The frontal sinus on the right side is rudimentary."

The advisability of a Naffziger orbital decompression operation was considered, but the formidable nature of the operation made us decide to try orbital and pituitary irradiation first in the belief that the pathogenesis of progressive exophthalmos in Graves' disease is most frequently, if not invariably, dependent upon a local inflammatory condition of the orbital tissues. The patient was therefore referred to the Radiation Therapy Department, Dr. I. Seth Hirsch, Director. Following a series

of five roentgen-ray treatments, 500 r of heavily filtered high voltage roentgen-rays. to each pituitary-orbital region, given between May 12 and June 6, 1937, improvement was noted (figure 12). The treatments were therefore continued and an additional dose of 500 r was given to each region. On July 7, 1937, a day after the series of roentgen treatments was completed, the protrusion of the right eye was



FIG. 12. Regression of exophthalmos following roentgen therapy to orbital and pituitary regions (June 18, 1937).

reduced from 30 to 29 mm., the conjunctival congestion was less marked and, subjectively, the patient felt greatly relieved. The improvement continued, the chemosis of the right conjunctiva lessened, the diplopia diminished and in September he felt sufficiently comfortable to resume his occupation, at which he has worked regularly ever since. In October the diplopia was present only occasionally. In November the conjunctival congestion was almost entirely gone and the diplopia was negligible and rarely present. His general health was good and he showed no evidence of thyroid disturbance. The exophthalmos showed further regression—right eye 27 mm., left 22 mm.—and the extra-ocular palsies were less marked.

COMMENT

The important points deserving emphasis in this case are:

1. The striking change in temperament as the main clinical manifestation of Graves' disease for nearly six months before the appearance of exophthalmos or other signs of the disease.

2. The absence of clinically perceptible thyroid enlargement in the presence of marked exophthalmos eight months after the onset of Graves' disease.

3. The presence of marked exophthalmos and other symptoms of thyrotoxicosis with comparatively low basal metabolism at the height of the disease. The highest basal metabolic rate before the preoperative use of Lugol's solution was only plus 25.

4. The presence of the histological pathology of active Graves' disease in the excised thyroid tissue. Despite the abundant preoperative administration of Lugol's solution (360 minims) over a period of 15 days, which brought the basal metabolism down to plus 12, the excised thyroid tissue still showed many areas of hypertrophy, hyperplasia, round cell infiltration and lymphoid hyperplasia—the characteristic histopathology of active Graves' disease. These microscopic findings unmistakably warn us that the preoperative use of iodine does not completely abate the pathologic change in the diseased thyroid gland in Graves' disease. Hence subtotal thyroidectomy in diffuse toxic, or exophthalmic, goiter does not remove all the diseased thyroid tissue. Although the surgeon may remove sufficient thyroid tissue to reduce the basal metabolism to a minus rate, the remaining pathologic tissue in the thyroid may continue to secrete an abnormal thyroid product or liberate an unknown noxious agent which may affect selectively various organs and tissues, among which the orbit has been a common site.

5. The development of progressive exophthalmos, right much more marked than left, three weeks after a successful thyroidectomy which produced marked general improvement and a drop in basal metabolism to minus 11.

6. The failure of the prolonged use of iodine and thyroid medication to control postoperative progressive exophthalmos with low basal metabolic rate. Following the use of Lugol's solution the basal metabolism dropped from minus 11 to minus 18 but the exophthalmos failed to recede. When, in addition, desiccated thyroid was given over a period of several months the basal metabolism rose from minus 18 to plus 13 with development of symptoms of hyperthyroidism and aggravation of the exophthalmos.

7. The favorable results obtained by roentgen-ray treatment directed to the orbital and pituitary regions. While no definite conclusion can be drawn from the treatment of this case alone, the equally encouraging results reported by Thomas and Woods of Johns Hopkins Hospital and Rudemann

of the Crile Clinic, make early roentgen-ray therapy to the orbital and pituitary regions a method deserving a further trial in the treatment of exophthalmos of Graves' disease whenever it becomes a clinical problem.

SUMMARY AND CONCLUSION

More than a century and a half after Parry first described exophthalmic goiter, the basic cause of the disease remains entirely unknown and a specific form of treatment has not been discovered.

Until such time as a specific method of treatment shall be discovered, we have to depend upon empirical methods of treatment—medical, radiotherapeutic or surgical.

Graves' disease, or exophthalmic goiter, is not synonymous with hyperthyroidism. Although it is usually accompanied by an elevated basal metabolism, it may also manifest itself with a normal, low or minus basal metabolic rate. Indeed, Graves' disease and myxedema may be associated at the same time. The most significant and distinctive striking feature of Graves' disease—*exophthalmos*—may be present not only with an elevated metabolism but also with a minus basal metabolic rate. Some of the worst forms of progressive exophthalmos with corneal ulceration and loss of both eyes have been observed in patients after successful thyroidectomy with control of general symptoms and a drop in basal metabolism to a minus rate.

In the vast majority of cases investigated pathologically, progressive exophthalmos in Graves' disease is not a purely functional condition induced by hyperthyroidism or hypothyroidism or a fanciful mutually-exclusive combination of hyperthyroidism-hypothyroidism. Although in some cases of postoperative progressive exophthalmos with low basal metabolic rate the combined use of iodine and thyroid medication produced a regression of the lesion, it failed to do so in the vast majority of reported cases, as it likewise failed in our own case.

The most frequent pathologic findings in progressive exophthalmos—preoperative or postoperative—have been those of an inflammatory condition of the orbital cellular tissues and hypertrophy or atrophy and degeneration of the extra-ocular muscles.

Until the introduction of the Naffziger decompression operation the usual medical and surgical methods had failed to cope successfully with the severe forms of postoperative progressive exophthalmos with low basal metabolic rate.

The favorable results of roentgen-ray treatment of the orbital and pituitary regions in cases of postoperative progressive exophthalmos with low basal metabolic rate suggest the early use of radiation therapy in combination with medical treatment for exophthalmos in Graves' disease whenever it becomes a distinct clinical problem. Only if adequate radiation therapy fails, should the Naffziger operation be considered in severe progressive exophthalmos.

REFERENCES

1. PARRY, C. H.: Collection from the unpublished medical writings, ii, 111.
2. DALRYMPLE, J.: The anatomy of the human eye, 1834, London, 266.
3. BASEDOW, C. A.: Exophthalmus durch Hypertrophie des Zellgewebes in der Augenhöhle, *Wchnschr. f. d. ges. Heilk.*, 1840, vi, 197-204; xxii, 220-228.
4. BEGBIE, J.: Anemia and its consequence. Enlargement of the thyroid gland and eyeballs etc., *Edinburgh Monthly Jr. Med. Sci.*, 1849, ix, 495-508.
5. COOPER, W.: On protrusion of the eyes, in connexion with anemia, palpitation and goiter, *Lancet*, 1849, i, 551.
6. BERNARD, C.: Leçons sur la physiologie et la pathologie du système nerveux, Paris, 1858, J. B. Balliere et Fils, Paris, v, 1-2, 499.
7. DEMARRES, M.: De l'exophthalmos produit par l'hypertrophie du tissu cellulo-adipeux de l'orbite, *Gaz. d. hôp.*, 1853, xxvi, 2-3.
8. STOKES, W.: The diseases of the heart and the aorta, 1854, Lindsay and Blakiston, Philadelphia, 280-281.
9. TAYLOR, R.: On anemic protrusion of the eyeball, *Med. Times and Gaz.*, 1856, i, 515-517.
10. GRAEFE, A. V.: Bemerkungen über Exophthalmus mit Struma und Herzleiden, *Arch. f. Ophth.*, 1857, iii, 278-307.
11. EGEBERG: Cited by HASKOVEC, L.: Der Exophthalmus bei der Basedowschen Krankheit, *Wien. klin. Rundschau*, 1906, xx, 719.
12. HERVIEUX: Cited by Haskovec, L.: Der Exophthalmus bei der Basedowschen Krankheit, *Wien. klin. Rundschau*, 1906, xx, 719.
13. ARAN: De la nature et du traitement de l'affection connue sur le nom de goitre exophthalmique etc., *Bull. de l'acad. de méd.*, 1860-1861, xxvi, 122.
14. LAYCOCK, TH.: Exophthalmos, Graves' or Basedow's disease, *Med. Times and Gaz.*, 1864, ii, 323-325.
15. TRAUBE, I., and RECKLINGHAUSEN, F. D.: Der Morbus Basedowii, *Deutsch. klin. Wchnschr.*, 1863, xv, 286.
16. FILEHNE, W.: Zur Pathogenese der Basedow'schen Krankheit, *Sitzungsb. d. phys.-med. Soc. zu Erlang.*, 1878, ii, 177-182.
17. JACKSON, H.: Discussion of Wilks', Samuel: notes on Graves' disease, *Trans. Ophth. Soc. U. Kingdom*, vi, 58-59.
18. BRISTOW, J. S.: Cases of Graves' disease, *Trans. Ophth. Soc. U. Kingdom*, 1886, vi, 39.
19. BUSCHAN, G.: Die Basedowsche Krankheit, 1894, Franz Deuticke, Leipzig und Wien.
20. JABOULAY: La section du sympathique cervical, *Lyon méd.*, 1896, xxxviii, 150-152.
21. RECLUS and FAURE: Resection bilatéral du grand sympathique cervical dans le goitre exophthalmique, *Ann. d'ocul.*, 1897, cxviii, 38-41.
22. EDMUNDS, W.: Experimental exophthalmos and enophthalmos, *Trans. Ophth. Soc. U. Kingdom*, 1900, xx, 243.
23. LANDSTROM, J.: Über Morbus Basedowii, 1907, P. A. Nordstet and Soner, Stockholm.
24. BIRCH-HIRSCHFELD, A.: Die Krankheiten der Orbita, in GRAEFE-SAEMISCH, *Handbuch der gesamten Augenheilkunde*, 1907, pp. 261-269.
25. FRÜND, H.: Die Glatte Muskulatur der Orbita und ihre Bedeutung für die Augensymptome bei Morbus Basedowii, *Beitr. z. klin. Chir.*, 1911, lxxiii, 755-775.
26. SATTLER, H.: Über die sogenannten Landstromschen Muskel und seine Bedeutung für den Exophthalmus bei Morbus Basedowii, *Ber. ü. d. Versamml. d. deutsch ophth. Gesellsch.*, 1912, xxxvii, 181.
27. TROELL, A.: Some attempts to produce exophthalmos experimentally, *Arch. Int. Med.*, 1916, xvii, 382-395.
28. WILSON, L. B.: cited by PLUMMER, W. A., and WILDER, R. M.: The etiology of exophthalmos, *Trans. Am. Acad. Ophth. and Oto-Laryngol.*, 1934, 41-64.
 PLUMMER, W. A., and WILDER, R. M.: Etiology of exophthalmos; constitutional factors, with particular reference to exophthalmic goiter, *Arch. Ophth.*, 1935, xiii, 833-852.

29. MOORE, R. R.: Note on the exophthalmos and limitation of the eye movements in Graves' disease, *Lancet*, 1920, ii, 701.
30. WHITNALL, S. E.: The anatomy of the human orbit and accessory organs, Ed. 2, 1921, Oxford University Press, London, 294.
31. PLUMMER, H. S.: The thyroid gland, 1925, C. V. Mosby, St. Louis, 81.
32. KUNDE, M. M.: Studies on metabolism: experimental hyperthyroidism, *Am. Jr. Physiol.*, 1927, lxxxii, 195.
33. LABBE, M., VILLARET, M., JUSTIN-BESANCON, L., and SOULIE, P.: Etude sur la pathogénie des exophtalmus du type Basedowien, *Bull. et mem. Soc. med. d. hôp. de Paris*, 1931, xlvii, 1897-1907.
34. GASTEIGER, H.: Über eine seltene Augenveränderung bei Schilddrüsenstörungen, *Wien. klin. Wchnschr.*, xlv, 887-889.
35. STEWENS, H.: Progredienter Exophthalmus nach Basedowoperation, *Ztschr. f. Augenheilk.*, 1931, lxxv, 137-145.
36. LOEB, L., and FRIEDMAN, H.: Exophthalmos produced by injections of acid extract of anterior pituitary gland of cattle, *Proc. Soc. Exper. Biol. and Med.*, 1931, xxix, 648-650.
37. CRILE, G. W.: Diagnosis and treatment of diseases of the thyroid gland, 1932.
38. MARINE, D., SPENCE, A. W., and CIPRA, A.: Production of goiter and exophthalmos in rabbits by administration of cyanide, *Proc. Soc. Exper. Biol. and Med.*, 1932, xxix, 822.
39. MARINE, D., ROSEN, S. H., and CIPRA, A.: Further studies on the exophthalmos in rabbits produced by methyl cyanide, *Ibid.*, 1932-1933, 649-651.
40. MARINE, D., and ROSEN, S. H.: The exophthalmos of Graves' disease. Its experimental production and significance, *Am. Jr. Med. Sci.*, 1934, clxxxviii, 565-571.
41. NAFFZIGER, H.: Discussion of KING, B. T.: The course of exophthalmos, *West. Jr. Surg., Gynec., and Obst.*, 1931, xxxix, 608-609.
42. NAFFZIGER, H.: Progressive exophthalmos after thyroidectomy, *Trans. Am. Assoc. Study of Goiter*, 1932, 189-202.
43. NAFFZIGER, H. C.: Pathologic changes in the orbit in progressive exophthalmos, *Arch. Ophth.*, 1933, ix, 1-12.
44. URECHIA, C. I., and MME. RETEZEANU: Dosage de quelques substances dans l'exophtalmie expérimentale, *Compt.-rend. Soc. de Biol. de Cluj.*, 1933, cxiii, 323-324.
45. VIALLEFONT, H., and LAFON, R.: Origine diencephalomesencephalique des signes oculaires de la maladie de Basedow, *Ann. d'ocul.*, 1934, clxxi, 495-507.
46. ZALKA, E. V.: Über die Veränderungen der äussern Augenmuskeln und ihre Bedeutung bei Morbus Basedowii, *Beitr. z. path. Anat. u. z. allg. Path.*, 1933-1934, xcii, 239-252.
47. DROUET, P. L.: Le rôle de l'hypophyse dans l'hyperthyroïdie et le syndrome parabasedowien, *Rev. franç. d'endocrinol.*, 1934, xii, 101-136.
48. BORAK, J.: Die Behandlung von Hyperthyrosen durch Röntgenbestrahlung der Hypophyse, *Strahlentherapie*, 1935, liii, 73-89.
49. THOMAS, H. M., JR., and WOODS, A. C.: Progressive exophthalmos following thyroidectomy, *Bull. Johns Hopkins Hosp.*, 1936, lix, 99-113.
50. SMESLER, G. K.: Experimental production of exophthalmos resembling that found in Graves' disease, *Proc. Soc. Exper. Biol. and Med.*, 1936-37, xxxv, 128-130.
51. FRIEDENWALD, J. S.: Discussion of NAFFZIGER, H. C.: Pathologic changes in the orbit in progressive exophthalmos, *Arch. Ophth.*, 1933, ix, 1-12.
52. ZIMMERMANN, L. M.: Exophthalmos following operation for the relief of hyperthyroidism, *Am. Jr. Med. Sci.*, 1929, clxxviii, 92-99.
53. BENEDICT, W. L.: Discussion of HOLLOWAY, T. B., FAY, D. E., and WENTWORTH, H. A.: Ocular signs in one hundred unselected cases of goiter, *Jr. Am. Med. Assoc.*, 1929, xcii, 35.
54. BURCH, F. E.: The exophthalmos of Graves' disease, *Minnesota Med.*, 1929, xii, 668.

55. ROEDER, C. A., and KILLINS, W. A.: Third type of toxic thyroidism, *Northwest Med.*, 1930, xxix, 395-404.
56. KING, B. T.: The course of exophthalmos, *West. Jr. Surg.*, 1931, xxxix, 602-609.
57. EARNEST, J. P., and SERGER, W. W.: A case of unilateral exophthalmos following thyroidectomy, *Virginia Med. Month.*, 1931, lvii, 808-809.
58. SEMMER, R. E.: Discussion of Clute and Veal: the end results of surgery in exophthalmic goiter, *Jr. Am. Med. Assoc.*, 1932, xcix, 642-647.
59. MERRILL, H. G., and OAKES, L. W.: Extreme bilateral exophthalmos. Report of two cases with autopsy findings in one, *Am. Jr. Ophth.*, 1933, xvi, 231-236.
60. CATTELL, R. B.: Eye complications in exophthalmic goiter. Cataracts and exophthalmos, *Ann. Surg.*, 1934, c, 284-303.
61. BOTHMAN, L.: The endocrines in ophthalmology, *Illinois Med. Jr.*, 1934, lxv, 226-235.
62. GOLDENBERG, M.: Progressive exophthalmos in thyroid disease. With report of a malignant case, *Am. Jr. Ophth.*, 1934, xvii, 692-698.
63. NORDLAND, M. O., and LARSEN, L. M.: Persistent and recurrent postoperative exophthalmos, *Am. Jr. Surg.*, 1934, xxiii, 330.
64. DES BRISAY, H. A.: Progressive exophthalmos following thyroidectomy, *Canad. Med. Assoc. Jr.*, 1934, xxxi, 389-392.
65. RYNEARSON, E. H.: Eye changes occurring after operation for exophthalmic goiter, *Proc. Staff. Meet., Mayo Clinic*, 1936, xi, 321-326.
66. RUDEMANN, A. D.: Exophthalmos, *Cleveland Clin. Quart.*, 1937, iv, 66-75.
67. GROSS, S. W.: Personal communication, 1937.

THE OCCURRENCE AND CLINICAL SIGNIFICANCE OF HEMOCONCENTRATION *

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Several years ago attention was called (Moon), to changes in blood concentration incident to shock. The accumulation of additional data, from clinical and experimental sources, justifies further consideration of this subject. The term *hemoconcentration* will be used to designate a rapid increase in the erythrocytic content of the blood. Some authors have shown concentration by increased specific gravity of the blood, and have given no data concerning the red cells. The specific gravity of red cells is higher than that of plasma, hence erythrocytosis raises the specific gravity of the whole blood. In order to include such observations in the discussion, the term hemoconcentration rather than acute erythrocytosis has been chosen.

Hemoconcentration is demonstrable either by hematocrit readings, by an elevated specific gravity of the whole blood, by an increased hemoglobin content or by an increased erythrocytic count. Before the development of laboratory methods, observers occasionally recorded that the blood was thick, dark and slow to clot. The conditions in which this observation was made were of the same type as those in which hemoconcentration has been demonstrated by laboratory methods in later times.

A *persistent* erythrocytosis occurs in certain forms of chronic cardiac deficiency, in emphysema, in those who live in high altitudes, in chronic carbon monoxide poisoning and in primary polycythemia, otherwise known as polycythemia vera. Those interested in these conditions will find them discussed in a monograph by Weber and in a review by Harrop.

In contrast to the conditions mentioned, a rapid marked increase in the erythrocytic count is a frequent event in acute illness of diverse kinds. This phenomenon has been imperfectly understood. Its occurrence and significance are not discussed in treatises on clinical medicine nor in the literature of hematology. Since no review on this subject has been published, it seems appropriate to assemble such observations as have been found and to consider their significance. Observations on hemoconcentration occur occasionally in clinical reports, and the titles of the articles give no indication of this feature. Hence the data presented here can not represent a complete review of the subject.

Hunter (1890) observed that the injection of a large amount of blood into the peritoneal cavity of animals was followed by a rapid increase in the specific gravity of the blood. This increase amounted to 40 per cent within three hours and "was accompanied by a condition closely resembling shock." He attributed the high specific gravity not to the absorption of the injected

* Received for publication September 12, 1938.

corpuscles, but to the escape of fluid from the blood. Sherrington and Copeman (1893) made an extensive study of the specific gravity of the blood under various experimental conditions. They recorded that in shock, induced by obstructing the circulation or by opening the abdomen and manipulating the viscera, the specific gravity of the blood was markedly increased. Conversely, the specific gravity declined progressively after hemorrhage (repeated withdrawals of blood by venepuncture).

Cobbett (1897) described a series of experiments in which the specific gravity of the blood was compared with arterial blood pressures after manipulation of the intestines of dogs. For a time the specific gravity was unchanged, but as edema and serous effusions developed, the specific gravity rose steadily and the blood became thickened so that it flowed with difficulty. For some hours after the specific gravity began to rise, the arterial pressure showed little or no sign of falling. When at last the blood pressure began to decline, it fell rapidly and death occurred soon. He noted that circulatory failure after abdominal operations, in peritonitis and after burns, is accompanied by similar alterations in the blood.

King (1902) noted an increase in red blood cells after surgical operations in a series of cases. He was puzzled by the fact that this occurred even when considerable blood had been lost incident to the operation. One case, which died in shock 36 hours after operation, had a numerical increase of 2,100,000 red blood cells. The increase was much less in non-fatal cases. He attributed the hemoconcentration to loss of fluid from the blood.

Vale (1904) recorded the specific gravity of the blood and tissues in experimental shock in animals and in human cases of shock from various causes. In experimental shock the specific gravity was increased and that of the tissues decreased, indicating an increased fluid content of the tissues and a consequent inspissation of the blood. Shock in human cases, resulting from trauma, burns, peritoneal inflammation and from other causes, was accompanied by an increased specific gravity of the blood. This returned to normal when recovery from shock occurred. Vale believed that the phenomena resulted from damage to capillary walls. He was the first author to suggest that variations in specific gravity of the blood present a practical means for distinguishing between shock and hemorrhage.

Crile (1909) recorded that in experimental shock the red cells are increased in number but after hemorrhage their number per unit volume is decreased. Henderson (1910) found the blood abnormally concentrated in shock and attributed it to the passage of serum out of the vessels into the tissues. Mann (1914) reported an increase in the specific gravity of the blood in shock.

During the World War intensive studies were made on shock, its nature and conditions of occurrence. Cannon, Fraser and Hooper made examinations of the blood which confirmed the observations previously cited. They found red cell counts ranging from 6,000,000 in mild shock to above 9,000,000 in severe shock. The hemoconcentration was progressive and

tended to be proportional to the degree of shock. Conversely, a decreased number of erythrocytes was found after hemorrhage and also in the blood of those who had served as donors for transfusions. Bayliss and Cannon found corresponding hemoconcentration in experimental shock in cats. M. C. Bazett found red cell counts of great value as indicating whether shock or hemorrhage was present, and in determining the condition of the patient and the operative risk. In Robertson's experience patients suffering from shock are to be distinguished from cases of hemorrhage, or from hemorrhage plus shock, by the presence of a high hemoglobin reading in the former.

These findings were confirmed by Keith who showed that a marked decrease in the total volume of blood is an outstanding feature of shock. This was due to a decrease in the plasma volume and was accompanied by hemoconcentration. He emphasized that in shock the normal processes of blood dilution fail to operate. In moderate shock the blood cannot absorb fluid from the tissues nor from the gastrointestinal tract, but the vascular walls are able to retain fluid if supplied in suitable form. In severe shock the vascular walls are unable to retain colloids or even whole blood. Fluids leak out into the tissues almost as fast as injected. Treatment in this class of cases was entirely ineffective.

Bainbridge and Bullen found the hemoglobin content reduced after hemorrhage and increased during shock. They advised this as a practical means for the differentiation of those conditions. They observed that the system is able to compensate for loss of blood by hemorrhage but that in shock this mechanism failed to operate. The mechanism of compensation is discussed in a subsequent section.

Erlanger, Gasser and their associates retarded mechanically the blood flow through the vena cava and, in other experiments, through the aorta. Shock resulted in either case after the obstruction to the circulation was removed. They produced shock also by large doses of adrenalin and by intestinal manipulation. By each of these methods in a large series of tests, they found a marked reduction of plasma volume, accompanied by hemoconcentration, as a regular feature. They regarded reduced plasma volume as the essential feature in the mechanism of shock, and attributed it and the hemoconcentration to transudation of plasma into the tissues. It was evident that retardation of the circulation, either mechanically or from maximal arterial constriction by adrenalin, produced anoxia in the tissues. It has been shown that capillaries become dilated, and their walls become abnormally permeable to colloids, when deprived of an adequate supply of oxygen.

Mason and associates produced shock in dogs by the autolysis of liver substance *in vivo*. Increased concentration, decreased plasma volume and delayed coagulation of the blood occurred regularly. Observations such as those cited led Moon and Kennedy to test the concentration of the blood in shock, occurring clinically or produced experimentally. Finding that

hemoconcentration appeared early before changes in blood pressure occurred, and that it increased progressively as shock developed, they used it as a criterion of the presence and of the degree of shock in all subsequent studies. They reported on the practical application of this simple test to clinical use in cases of poisoning, infections of unusual severity, hemorrhagic pancreatitis, eclampsia, and of burns. These died of circulatory failure and the blood was highly concentrated as shown by specific gravity, hemoglobin content and erythrocytosis. They concluded that hemoconcentration is proportional to the degree of shock, that it is of value in detecting that condition clinically, in estimating the degree of it and in differentiating it from hemorrhage.

Coonse and his associates corroborated Moon's observations in experimental shock and confirmed the fact that hemoconcentration is characteristic of that condition, while after hemorrhage the blood is diluted.

Blalock and associates found increased concentration of the blood during shock induced by trauma to muscles, by burns of the skin and by intestinal manipulation. They attributed it to local leakage of plasma into and about the areas of injury. Harkins reported nine cases of mesenteric vascular occlusion resulting in shock. He found the hemoglobin was 143 per cent and the hematocrit reading 61, although no vomiting had occurred, in one case. No blood studies were made in the others. Harkins and Harmon reported experiments on animals and observations in human cases, in which hemoconcentration was noted, associated with shock-like circulatory deficiency. This occurred after burns, freezing, bile peritonitis, tissue autolysis in vivo, acute pancreatitis, pulmonary edema, intestinal manipulation, mesenteric and portal obstruction, intestinal strangulation and after the release of an extremity from a constriction. They investigated also the shock-like circulatory failure which develops incident to acute peritonitis, experimentally produced. They found the bleeding volume and the concentration of the blood were like those produced by other vascular poisons such as histamine. Andrews, Harkins, Harmon and Hudson produced shock by subcutaneous injections of bile in dogs. These developed symptoms of surgical shock, ending in death. There was a marked increase in the volume of red cells, shown by hematocrit readings, in every case. They recorded marked local swelling and transudation of fluid about the site of injections, but neglected to record observations on the appearances of the viscera.

The authors quoted in the preceding paragraph adhere to the interpretation that *local* transudation of plasma into the tissues about the injured area causes the abnormal concentration of blood, and that shock is due entirely to such local loss of blood and/or fluid. This interpretation is contrary to the evidence of increased capillary permeability in *systemic* areas, shown in vivo and post mortem. Injections of colloidal dyes, such as trypan blue, are used extensively in studies on capillary phenomena. Such dyes are retained in the circulation under normal conditions, but they escape and

stain the tissues where capillary permeability is increased. When trypan blue is injected intravenously during the development of shock, the staining is not limited to the injured areas but involves viscera areas remote from the injury. Also examinations of the viscera, after death by shock, show wide-spread capillary dilatation, stasis and petechiae in the lungs, mucosae, serosae and in parenchymatous organs. Although these observations on the pathology of shock were published years ago, many workers apparently are not cognizant of them (Moon).

Kopp and Solomon observed a decrease in the plasma volume and an increase in hematocrit readings during shock resulting from therapeutic hyperthermia. At post mortem in one fatal case the congestive, hemorrhagic and edematous changes in lungs, gastrointestinal tract and elsewhere, agreed with those noted by Hartman and Major in two similar cases, and with the pathology of shock as stated by Moon. They attributed the circulatory failure to decreased blood volume, increase in the vascular stream bed and increased vascular permeability.

Scudder and his associates investigated the increased potassium content of the blood in shock resulting from various causes. Incidentally they noted that this was accompanied by a rise in the specific gravity of the whole blood and by an increased volume of red cells. These changes were noted in shock produced by trauma, by intestinal obstruction seen in clinical cases and by experimental intestinal obstruction in animals.

Walther noted concentration of the blood and loss of plasma as characteristics of true shock. He observed that the hemoconcentration subsided when recovery from postoperative shock occurred. Allen produced shock in rats by obstructing, with a rubber band, the circulation of a leg. After five or six hours of obstruction, the removal of the tourniquet was followed by the development of shock. In these experiments Allen used hemoconcentration as a criterion of shock. The red cells progressively increased from 8 million to 10, 11 or 12 million at death. It was noted that the blood was dark and thick and that clotting was delayed.

Eppinger gave detailed consideration to circulatory collapse developing in a wide variety of clinical conditions. They included trauma, burns, severe infections, poisoning with various drugs and from food, sun burn, toxic jaundice, diabetic coma, urticaria and others. The total volume of blood was decreased in such cases. In each instance he found that the heart was not dilated but, on the contrary, was smaller than normal. This resulted from the diminished volume of blood and from decreased return of venous blood to the heart. He found hemoconcentration in all cases of shock or collapse regardless of the condition causing it. This was explained as due to increased permeability of the capillary membranes, with resulting leakage of plasma into the intercellular spaces.

Many of the conditions seen clinically were reproduced in dogs, and the physiologic disturbances were of the same kind as seen in man. Microscopic studies of various tissues showed albuminous fluid in the intercellular

spaces regularly. This fluid had a high protein content like that of the blood plasma. The increased permeability of the endothelium, which resulted in a leakage of plasma and in hemoconcentration, was regarded as of such essential importance that it constituted the title of his monograph "*Die seröse Entzündung.*"

Although the term "serous inflammation" was used by Rössle to designate the presence of serous fluid in intercellular spaces unaccompanied by leukocytic infiltration, its use in such a sense is questionable. The presence of leukocytes is usually regarded as a *sine qua non* of inflammation, and the term edema is used by other pathologists to designate the feature which Rössle described. The fact that the fluid has a high protein content does not make the word edema inappropriate. It is feared that the term "serous inflammation," as applied to this condition, may contribute to confusion rather than to clarification. Notwithstanding this deviation from accepted terminology, Eppinger's observations and deductions are highly significant.

Seeley, Essex and Mann produced shock in dogs to determine the contributory effects of various anesthetics. They recorded hemoconcentration in each instance.

BLOOD CONCENTRATION AFTER BURNS

The earliest observations on hemoconcentration which I have found were made in clinical studies on patients suffering from extensive burns of the skin. Baraduc (1863) noted in such cases that the blood was dark, thick and that it failed to clot. He believed this change was related to the mechanism by which death occurred; that the thick viscid blood could not circulate through the minute vessels and that this resulted in death by circulatory failure. Tappeiner (1881) reported counts ranging from 7,810,000 to 8,960,000 in from 6 to 17 hours after burns in four cases which resulted fatally. Wilms (1901) confirmed the previous observations and recorded cell counts ranging from 6,500,000 to 8,200,000 in six persons severely burned. Locke (1902) reported blood counts in ten such cases. The highest count in four non-fatal cases was 7,266,000 while in five of the six fatal cases the erythrocytes were above 9,000,000. He recorded that the blood was dark and thick. Becky and Schmitz, Underhill et al., Simonart, Moon, Wilson et al., Harkins and others have confirmed that marked hemoconcentration occurs immediately after severe superficial burns of the skin.

Underhill and his associates reported blood studies in 20 cases of severe superficial burns. Marked hemoconcentration was found in each instance as indicated by hemoglobin percentages ranging from 114 per cent to 226 per cent. The higher concentrations were found in the more severe cases. The condition was associated with a decreased return of blood from systemic areas, and decreased volume output of the heart. This resulted in systemic anoxia, lowered metabolic processes, low arterial pressure and final

suspension of vital activities. He believed that hemoconcentration is a prime factor in the development of shock from burns. He stated that the degree of concentration is an index of the patient's condition, that neither man nor animals can long survive hemoconcentration of 40 per cent and that the condition becomes precarious at 25 per cent.

Wilson and associates corroborated the fact that shock following burns is indistinguishable from that which results from severe trauma. They saw no reason to doubt that the etiology is similar. They noted that, in shock following burns, there develops a toxemic stage which resembles violent poisoning. In their cases the increase in the hemoglobin ranged from 15 to 150 per cent.

Ebbecke showed that any type of injury to cells, whether thermal, chemical or mechanical, causes them to release a cytoplasmic substance which produces dilatation and permeability of the adjacent capillaries. This results in local edema due to leakage of fluid from the blood into the tissues. If the injury is small and local, this effect is likewise local; but if the injury is extensive, much of the cytoplasmic substance may be absorbed and may produce a similar effect on the minute vessels in systemic areas. This results in a systemic disturbance of the circulation, characterized by low blood volume, increased concentration, reduced return of venous blood from systemic areas, and consequent low cardiac output. He drew a significant comparison between the capillary phenomena about local injuries and those in shock. If one understands the mechanism by which wheals are formed in the skin by mechanical injury, burns, histamine, peptone or anaphylaxis one likewise understands shock produced by extensive trauma, burns, histamine, peptone or anaphylaxis. They result from identical capillary reactions, the one in local areas, the other in visceral or systemic areas.

The researches of Lewis on vascular phenomena in the skin corroborated and extended somewhat those of Ebbecke. He demonstrated that substances released by cells in response to injury affect the capillaries as described by Ebbecke. He called these "H-substances" because of the similarity of their effects to those of histamine. He endorsed the interpretation that the absorption of such substances in large amount produces systemic circulatory disturbances. "These effects lead to an impounding of the blood in the capillary reservoir accompanied by a serious loss of blood fluids into the tissue spaces. Owing to this diversion of the blood the central vessels are depleted, a profound and lasting fall of blood pressure follows, leading to a condition of collapse." Krogh endorsed this explanation of the circulatory collapse which results from extensive superficial burns.

This interpretation is further corroborated by the finding post mortem of effusions in the serous cavities, marked congestion of the minute vessels in visceral areas, ecchymoses indicative of capillary injury, and edema of the lungs, gastrointestinal mucosae and meninges after burns. (Schjer-

ning, Bardeen, Pack, Moon and others.) Such findings indicate that the hemoconcentration is not due entirely to local transudation in and about the injured areas.

ALLERGIC AND ANAPHYLACTOID CONDITIONS

Hemoconcentration has been noted by several observers in the group of conditions associated with hypersensitivity to various proteins. Dean and Webb made observations on changes in the blood of 33 dogs during anaphylaxis. They recorded a rise in the hemoglobin content and red cells after the injection of horse serum into sensitized dogs. The hemoconcentration seemed to be proportional to the severity of the symptoms. Simonds found an increased blood concentration and a reduced total blood volume during anaphylactic shock in dogs. Similar findings were recorded after injections of peptone. In this connection it is of interest to recall Dale's observations on the effects of histamine. Although it has not been proved that histamine itself is the cause for either anaphylactic shock, traumatic shock or peptone poisoning, it is believed that the mechanism of the effects is identical.

Underhill et al. compared the effects of histamine with those of Vaughan's crude soluble poison and those of peptone. Each of these caused an immediate fall in blood pressure when injected, and after each there was marked hemoconcentration. Vaughan's soluble poison, which is derived by partial hydrolytic cleavage of protein, produced the severest effects in this comparison. Underhill interpreted these effects as the result of capillary damage.

Cantacuzene found that large doses of hemolytic serum (rabbit hemolysin) caused immediate death when given intravenously to rabbits. Minute doses (0.03 to 0.1 c.c.) caused acute erythrocytosis ranging from 8,000,000 to 9,000,000.

Eppinger noted hemoconcentration associated with urticaria in one case. The red cell count rose from 4,400,000 to 5,700,000 at the height of an urticarial eruption. Black and Kemp induced an acute allergic response by instilling pollen into the nostrils of a sensitive person. This was accompanied by an increase in the specific gravity of the blood from 1.0561 to 1.0578. They found a similar increase in the density of the blood in 18 guinea pigs during anaphylaxis. It was stated that the degree of this increase was roughly parallel to the intensity of the reaction.

It is recalled that anaphylaxis is a true example of shock. Manwaring stated the belief that endothelial permeability is the dominant physiologic change in all types of protein sensitization and that all other anaphylactic reactions are secondary to this. Seegal's review of the subject led to the conclusion that the manifestations of anaphylaxis are referable to one or the other of two causes: contraction of smooth muscle, and increased capillary permeability. Lewis has emphasized the latter as the major factor and attributes it to the release of H-substance incident to the meeting of antigen and antibody within the tissue cells.

Although the mechanism of anaphylaxis has not been explained fully, it is apparent that increased endothelial permeability is a major associated feature. The hemoconcentration which has been observed in histamine and peptone poisoning and following injections of other protein cleavage products, is present also in anaphylactic and allergic states. This appears to be due to abnormal permeability of capillary endothelium.

POISONOUS SUBSTANCES

Krogh showed that capillaries may be injured directly by various substances, and Landis showed that any agent or condition injurious to capillary endothelium renders it abnormally permeable to the fluid of the blood. Sollmann stated that irritant or corrosive poisons cause extensive vascular dilatation in visceral areas, and that death may occur from shock incident to this effect before the symptoms characteristic of that poison have time to develop. Eppinger included poisoning with veronal, mercuric chloride and other poisons in his observations on shock. He noted that decreased blood volume, decreased volume flow, low blood pressure and hemoconcentration were present in such cases. He attributed these features to endothelial damage resulting in escape of plasma into the tissues. With these facts in mind it is pertinent to consider instances in which erythrocytosis has resulted from the effects of poisons.

It is known that acute poisoning with phosphorus often ends in circulatory collapse. Early observers recorded red cell counts above 8,000,000 in such cases (Taussig, v. Jaksch, Limbeck and others). Silbermann reported on polycythemia in phosphorus poisoning seen clinically in Prague. He stated that the acute effects of phosphorus poisoning include the development of polycythemia. In 34 acute cases the red cell counts were above 6,000,000 and in three cases there were more than 8,000,000. Hemoconcentration in poisoning is usually attributed to dehydration by vomiting. The merits of this explanation will be discussed in a subsequent section. Underhill noted that phosgene, among other lethal gases, caused massive edema of the lungs of those who inhaled it. The blood became concentrated because of damage to the endothelial membranes and the resulting escape of fluid into the pulmonary spaces. In this instance the capillary damage was chiefly in the lungs. The effects of other poisons (croton oil, jalap) may be chiefly in the gastrointestinal tract, and they likewise cause hemoconcentration. In still other instances to be discussed, the capillaries in systemic areas are damaged and the effects on the blood and on the circulation are of a similar kind.

Sollmann states that poisoning with arsenic produces a pronounced and persistent fall in blood pressure. This is not due to cardiac failure nor to vasomotor deficiency but he attributes it to paralysis of the capillaries with resulting loss of blood volume by transudation of plasma. It is recalled that Heubner and also Krogh list arsenic among the "capillary

poisons." Many years ago Rogers observed that arsenical poisoning produced circulatory collapse like that of cholera, accompanied by marked hemoconcentration. Red cell counts above 8,000,000 were noted. He recommended this as a diagnostic sign in arsenical poisoning. The shock-like features which sometimes result from intravenous arsenical medication are well known. Moore recorded weakness, grayish cyanosis, cold clammy skin, nausea, vomiting and syncope as the clinical features in such instances. The blood pressure fell alarmingly and sometimes was unobtainable. He noted further that the blood volume was reduced and that hemoglobin and erythrocytes were correspondingly increased, indicating concentration.

Various organic substances will produce circulatory deficiency of the shock type, accompanied by increased concentration of the blood. Dale and associates showed that in histamine shock the plasma volume is decreased by 50 or 60 per cent and the red cells are correspondingly concentrated as shown by counts, hemoglobin content and hematocrit readings. They explained this as the result of endothelial injury and regarded the effects of histamine as typifying those of other substances such as peptone, products of protein cleavage, bile, bacterial toxins and the like. Peptone shock is accompanied by hemoconcentration (Underhill and Ringer, Simonds, Eppinger, Moon and others).

Injections of bile intravenously, intraperitoneally or subcutaneously, will result in shock. This is accompanied by marked concentration of the blood (Horall and Carlson, Harkins, et al.). Sodium glycocholate will produce similar effects (Moon and Morgan). The venoms of various snakes cause endothelial injury and affect the circulation as does histamine. Marked hemoconcentration is a feature in such experiments (Kellaway, Essex and Markowitz, Moon).

Lipsitz reported a case of accidental poisoning with tincture cantharides. Weak rapid pulse, subnormal temperature, thirst, vomiting and low blood pressure were prominent clinical features. The red cell count reached 10,430,000. This subsided to normal as the condition progressed to recovery. Cantharis, given by stomach tube to rabbits, produced "polycythemia" of several days' duration. In one instance the erythrocytic count rose from 5,560,000 to 9,800,000. Morgulis and Muirhead made further studies on the effects of cantharis on dogs and rabbits, and substantiated hemoconcentration as one of the features. After fatal poisoning the visceral changes noted were identical in kind with those later described by Moon as characteristic of shock.

The shock-like effects of adrenalin were mentioned in a preceding paragraph. Bainbridge and Trevan noted a decrease in plasma volume, increased concentration of the blood and declining blood pressure after the slow injection of large doses of adrenalin in dogs. The circulatory effects were like those of histamine. In one instance the hemoglobin increased from 95 to 120 per cent and the viscosity of the blood rose from 6.8 to

9.1. Edmunds and Nelson, Freeman and others have found that large doses of adrenalin caused hemoconcentration due to loss of plasma volume. Lamson noted a rapid marked increase in erythrocytic counts after injections of epinephrine. He stated that all conditions of acute polycythemia are due to concentration of the blood by fluid loss. This loss might occur: (1) because of endothelial poisoning, as by histamine, with leakage of plasma into the tissues; or (2) local irritation with loss of fluid, as in the diarrhea of cholera or the pulmonary edema of gas poisoning.

Other poisons such as para-phenylene-diamine produce tissue edema and hemoconcentration by increasing endothelial permeability (Hanzlik and Tainter). Kilgor recorded occupational dye poisoning resulting in sub-normal temperature and low blood pressure but without diarrhea or vomiting. In one such case with fatal outcome, the count of red cells rose from 4,416,000 to 9,100,000. Hamilton recorded moderate hemoconcentration in several types of occupational poisoning. Davis noted an increase of about 20 per cent in the erythrocytes in experimental sublethal cobalt poisoning in dogs.

The instances cited indicate that a varied group of chemicals and drugs possess the property of causing damage to endothelium. This effect causes circulatory deficiency of the shock type, which is accompanied by hemoconcentration.

INFECTIONS AND OTHER CONDITIONS OF INTOXICATION

Circulatory deficiency often occurs as a terminal event in infections of unusual severity. Physicians since early times have attributed this to vasomotor or cardiac deficiency, 'myocarditis' and the like. Romberg and Pässler (1899) were the first to show experimentally that the efficiency of the heart is not impaired in such conditions.

Not many observations on erythrocytosis during severe infections and intoxications have been found. The earliest report I have seen was by Giesbock (1905). He noted that influenza with low blood pressure in young subjects was accompanied by erythrocytosis. The highest count recorded was 8,700,000. A patient with gangrene of the leg was found to have 8,000,000 red cells per cu. mm. Underhill and Ringer reported blood studies in 43 cases of influenza. The hemoglobin content ranged from 110 per cent to 140 per cent in severe cases, all of which ended fatally. There was no instance of hemoconcentration in any patient who recovered. They stated that this feature is a valuable sign in prognosis. Moon recorded red cell counts of 6,000,000 to 8,000,000 in severe influenzal infection.

It is well known that diphtheritic infection may terminate by circulatory collapse. This is usually attributed to myocardial weakness. Brodie (1899) tested the effects of diphtheria toxin in cats. Injections of this caused a decline in blood pressure ending in death. When animals were

dying from a fatal dose, given 36 hours before, he was able to keep the heart alive and beating for an hour or two after the death of the animal by perfusing the heart with defibrinated blood. MacCallum performed similar experiments on dogs with like results and concluded that the working capacity of the heart under the influence of lethal diphtheritic intoxication is as good as that of the normal heart.

Harding made intensive studies of diphtheria as seen in over 800 clinical cases. She noted that the circulatory deficiency seen in the toxemic stage closely resembled that in wound shock. The total blood volume and cardiac output were markedly reduced and hemoconcentration was shown by increased specific gravity and red cell counts. The highest concentration was found in the severest cases. She cited similar observations by others. Marked subcutaneous edema developed in many instances. The edema fluid had a high protein content like that of the blood plasma. This was interpreted as due to abnormal permeability of the endothelium resulting from the effects of diphtheria toxin. Anoxia was assigned as a contributory factor.

Early observers noted that the blood of patients severely ill with cholera was thick, dark and viscid. They attributed this to excessive loss of fluid by diarrhea. Later writers have confirmed this observation and interpretation. Frequently the red cell counts range between 8,000,000 and 9,000,000 (Rogers, Crowell). These authors were able to reduce the mortality from cholera by about 50 per cent by giving repeated infusions of saline solution. This fact indicates that simple dehydration is the chief cause of hemoconcentration, low blood volume and failing circulation in cholera. It also indicates that the mechanisms of circulatory failure in cholera and in other forms of shock are not identical, for when similar hemoconcentration, blood volume and low blood pressure are present in shock from other causes, neither saline solution nor any other fluid is effective. The capillary walls appear incapable of retaining fluid supplied in any form (Keith).

Circulatory failure, having all the features of shock, develops in dogs several days after bilateral adrenalectomy. This is accompanied by hemoconcentration as in other instances of shock. (Swingle et al.; Rogoff and Stewart; Winter and Hartman.) The animals may be restored to a normal physiologic state by injections of adrenal cortical extract, and the blood returns to its normal cellular composition. Rowntree reported on 43 cases of Addison's disease. In advanced stages there was decreased blood volume, progressive decline in blood pressure and other shock-like manifestations. Examination of the blood showed hemoconcentration in several such instances.

Barnard (1907) noted that circulatory collapse is one of the characteristic features resulting from intestinal obstruction. He stated that the blood becomes concentrated and viscid and quoted Nothnagel as estimating a concentration of 24 per cent with a correspondingly high hemoglobin

content. Cope recorded a case in which the red cell count was 7,600,000 although the blood pressure had not as yet declined. He stated that this feature indicated a decreased blood volume, and indicated the onset of shock more reliably than the blood pressure.

The fact that intestinal obstruction causes concentration of the blood has been confirmed by many investigators and is accepted as a characteristic feature, particularly after infarction, volvulus or strangulation. Many writers have explained this as due to dehydration by vomiting and consequent loss of fluid volume from the blood. It may be questioned whether this alone is the entire cause. Moon and Morgan found evidences of capillary injury such as edema, effusions and ecchymoses in extensive visceral areas after experimental strangulation of the jejunum in dogs. The edema fluid had a high protein content like that of plasma. The concentration of the blood was increased by 30-40 per cent. In a few experiments they injected trypan blue intravenously when hemoconcentration was developing. The escape of the dye into various tissues in the thoracic and abdominal regions indicated injury to capillary endothelium in systemic areas.

Another phase of evidence should be considered with reference to dehydration by vomiting. Several workers have shown that prolonged vomiting produced by injections of apomorphine will not reproduce the symptoms of intestinal obstruction in dogs. Morgan and I have made several such experiments incidental to studies on hemoconcentration. Water and food were withheld from dogs for 12 hours prior to and during the experiments. The dogs were weighed carefully, and blood examinations made, immediately before and after the experiments. Apomorphine was given by injection repeatedly until loss of weight ranging from 3 per cent to 5 per cent of the body weight resulted. The vomitus was much more voluminous than we have ever seen result from intestinal obstruction. Yet the blood was not concentrated in the slightest degree after such rapid loss of fluid.

The evidence indicates that loss of fluid by vomiting is not the entire cause for hemoconcentration incident to high intestinal obstruction. It appears that marked loss by vomiting will not cause dehydration of the blood so long as the physiologic mechanism which controls the movement of fluid between the blood and the tissues, is not disturbed in its function. It also appears that extensive injury to endothelium interrupts the operation of this mechanism.

Clinical descriptions of the symptoms and course of acute pancreatitis indicate that severe cases usually develop the shock syndrome. "Of the existence of shock in acute pancreatitis there is never the slightest doubt" (Deaver). Only a few records of red cell counts in this condition have been found. De Takats and Mackenzie reported on the clinical features in a series of 30 cases. Red cell counts had been made in nine of these, and showed concentration of the blood in each instance. The highest

count recorded was 8,300,000, ten hours after the onset of pancreatitis. I have reported one case in which there were 6,400,000 red cells per cu. mm. on admission to the hospital. No subsequent counts were made. The patient died in collapse 48 hours later and the necropsy findings were those which characterize shock.

Circulatory failure or collapse sometimes occurs as a terminal event in the toxemias of pregnancy. Adair and Stieglitz stated that this is similar to surgical or anaphylactic shock. De Lee confirmed the occurrence of circulatory failure resembling shock as a grave complication of pregnancy. He recorded a red cell count of 9,000,000 in one such instance.

THE MECHANISM OF SHOCK AND OF COMPENSATION

The circulatory deficiency, which manifests itself in the syndrome of shock, results from a disparity between the volume of blood and the volume capacity of the vascular system. That disparity may originate in either one of two factors, usually in a combination of the two. These factors are: (a) conditions which tend to reduce the volume of blood and (b) those which increase the volume capacity of the vascular system.

(a) The important conditions which tend to decrease the total blood volume are: direct loss of blood by hemorrhage, loss of fluid by perspiration, vomiting and purging, loss of plasma by transudation about the injury and in visceral areas as edema and serous effusions.

(b) An increase in the volume capacity of the vascular system may result from dilatation of any part of it. The heart, arteries and arterioles have not been found dilated in shock from any cause. The large veins are flaccid and only partly filled, but the capillaries and venules are found engorged and greatly distended. It appears that dilatation of these, in extensive visceral areas, is the chief factor causing increased volume capacity of the vascular system.

The physiologic mechanism by which decreased blood volume is compensated and disparity prevented, likewise consists of two main factors: (a) Reduction of the capacity of the circulatory system and (b) restoration of lost volume.

(a) The volume capacity of the vascular system is reduced physiologically by constriction of its various parts. Apparently this is a vasomotor reaction affecting the arteries, veins, heart and reservoir organs especially the spleen. The heart is decreased in size as shown by roentgen-ray and by diagraphic measurements (Eppinger). The arteries are maximally contracted and the spleen is reduced in size. The peripheral veins become collapsed and bloodless so that sometimes it is difficult to obtain blood by venepuncture. Under normal conditions the capillaries and venules may be constricted likewise but under adverse conditions, including the effects of poisons, toxins, irritants and even partial anoxia, the capillaries may become atonic and unresponsive to stimuli which cause normal capillaries to contract.

(b) The reactions which tend to restore the reduced volume include the discharge of blood from reservoirs, such as the spleen, and the absorption of fluid from other sources. The latter is the chief means for compensating loss of blood volume. It includes the fluid absorbed from tissues, resulting in their relative dehydration, and that supplied through the natural route—the gastrointestinal tract.

The same mechanism of compensation is operative after loss of blood by hemorrhage and in the circulatory deficiency of shock. Under normal conditions a moderate loss of blood volume as by hemorrhage is quickly compensated. But when damage to capillary endothelium has occurred there is a serious disorganization of physiologic processes. Some of the forces concerned with the movement of fluid into the tissues from the blood, and vice versa, are capillary blood pressure, molecular and ionic concentration, electric potentials, hormonal substances and osmotic pressures. These forces are concerned in the maintenance of "water balance," of blood concentration and volume. Their physiologic action is conditioned upon the presence of a normal semi-permeable endothelium between the blood and the extra-vascular fluids and tissues. Alterations in the condition of the endothelium disturb seriously the physiologic mechanism (Landis) and interrupt the processes described. Under such conditions the process of absorption is reversed. Instead of gaining fluid to restore lost volume, the blood actually loses fluid which is demonstrable as edema and effusions.

Fluid is lost also by vomiting, purging and perspiration. But, except under extreme conditions such as the diarrhea of cholera or after prolonged deprivation of water, this loss of fluid is at the expense of the tissues. Profuse vomiting, produced by apomorphine in animals, does not increase the concentration of the blood, nor is it affected by catharsis, by saline purgatives or by castor oil. Hunt found no change in the concentration of the blood when marked loss of weight resulted from perspiration in a Turkish bath. Cohn found that profuse perspiration incident to muscular exertion did not increase the hemoglobin content of the blood.

The blood is maintained at a remarkably constant level of concentration so long as the forces concerned with preserving fluid balance have a normal endothelial membrane through which to operate. The effects of various noxae upon capillary endothelium destroy its function of maintaining a physiologic differential between the composition of the intra- and extra-vascular fluids. These effects not only stop the machine, they wreck the machinery.

Bazett, in analyzing the mechanism of compensation, recognized damage to the capillary walls and anoxia as important factors in producing irreversible circulatory deficiency. The speed of the collapse and the rapidity of declining blood pressure, when compensation fails, were described as striking phenomena. The precipitous decline in blood pressure incident to failing compensation is shown in charts 1, 2, 3 and 5.

ADDITIONAL EVIDENCE

It was thought pertinent to produce damage to endothelium in extensive areas by various agents and to note the effects on the concentration of the blood. In some instances continuous blood pressure readings were made for comparison. One method was as follows: A normal dog was anesthetized and bled to death. A quantity of muscle was excised from the thighs and was ground finely in a meat chopper, weighed and suspended in saline solution. Aseptic precautions were employed throughout. A nor-

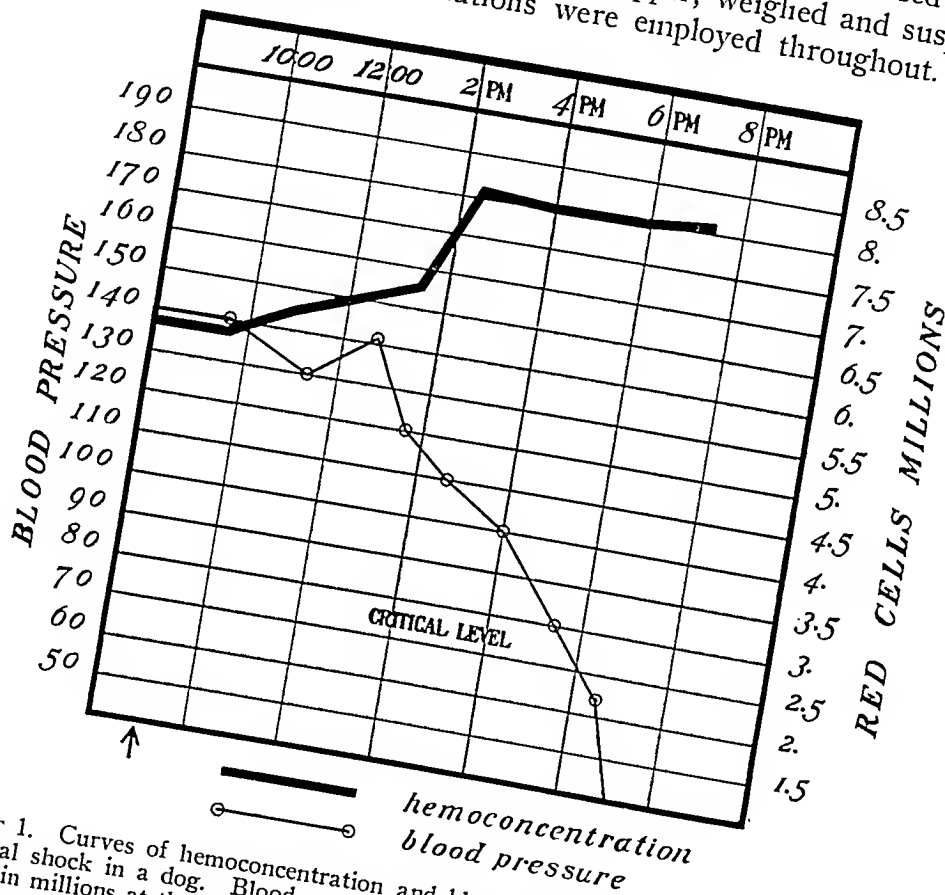


CHART 1. Curves of hemoconcentration and blood pressure during the development of experimental shock in a dog. Blood pressure in mm. of mercury is shown at the left, red cell counts in millions at the right, and clock time at the top of the chart. Muscle pulp was placed in the peritoneum at 9:00 a.m. (indicated by arrow). A temporary decline in blood pressure between 9:40 and 11:20 probably indicates the effect of decreasing blood volume and increasing volume capacity of the vascular system. The rising arterial pressure between 11:20 and 12:45 indicates effective compensation. The hemoconcentration reached its maximum at 2:20, 3½ hours before the blood pressure declined to the critical level. Then the pressure fell precipitately indicating total decompensation. Death occurred at 7:20, about 10½ hours after the experiment was begun.

normal dog was held under continuous ether anesthesia through a tracheal tube, and a mercury manometer was connected to a canula in the carotid artery. Minced muscle substance, 4.0 gm. per kg. of body weight, was introduced directly into the abdominal cavity through a short incision. The conditions of this experiment were arranged to approximate those

of shock developing from an extensive injury to muscles in man. There was opportunity for absorption of cytoplasmic substances emanating from the mass of damaged muscle tissue in the peritoneal cavity.

Counts of the red cells and hemoglobin determinations were made immediately before and at intervals after the operation. Progressive concentration of the blood began almost immediately and had reached a degree of over 15 per cent three hours later, at which time the blood pressure was at its highest point. The hemoconcentration had reached its maximum almost four hours before the blood pressure had declined to a critical level (70 to 80 mm. of mercury). The curves of the hemoconcentration and blood pressure are shown graphically in chart 1. Repetitions of this experiment gave uniformly similar results. In every instance the maximum concentration of the blood occurred several hours before the blood pressure sank to the critical level.

I have had opportunity to compare hemoconcentration with blood pressure readings in a number of clinical cases during the development of circulatory deficiency of the shock type. In each instance examination of the blood forecast the development of shock several hours to several days before the blood pressure declined notably. A few instances will be cited.

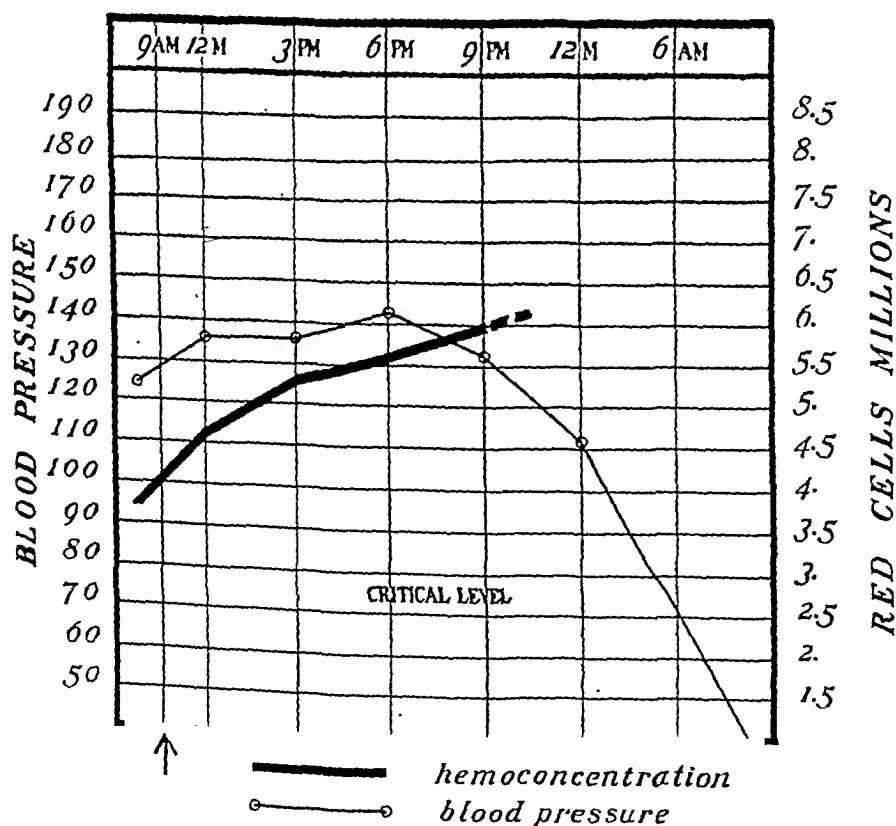


CHART 2. Curves of hemoconcentration and blood pressure during the development of surgical shock. In this instance the concentration of the blood indicated impending circulatory deficiency at 12:00 m., which was 12 hours before the arterial pressure gave a similar indication. The mechanism of compensation apparently was adequate until about 9 p.m., by which time hemoconcentration of 60 per cent had developed.

A white woman 54 years of age had been prepared for colonic resection by a previous colostomy operation. The resection under ether anesthesia was begun at 8:00 a.m. and was finished in 35 minutes. The patient's condition as indicated by pulse, respiration and blood pressure was satisfactory on return to her room. The blood pressure was not only well maintained, it actually *increased* for several hours, so that at 6:00 p.m. it was at its highest point. Meanwhile hemoconcentration had developed steadily (chart 2). The erythrocytic count rose from 3,820,000 before the operation to above 5,500,000 nine hours later—a concentration of more than 50 per cent. The concentration of the blood three hours after the operation forecast the impending circulatory collapse 12 hours before compensation failed. Death occurred by shock 26 hours after the operation.

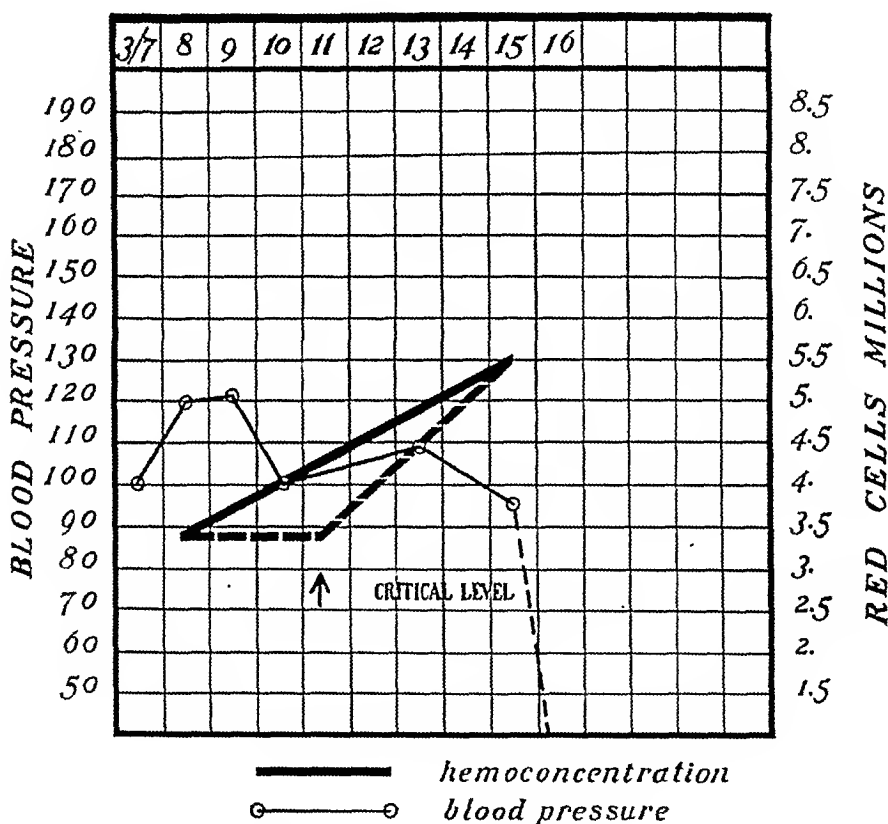


CHART 3. Curves of hemoconcentration and arterial pressure in shock of gradual development. Time is shown in days. Colostomy was done on March 11 (arrow). Only two counts of erythrocytes were made. The heavy solid line connects them. It is probable that the heavy broken line represents the actual course of the concentration. The arterial pressure was at 96 mm. at noon on March 15, the last reading recorded. Decompensation probably occurred about that time. Death occurred at 2:00 a.m. on the sixteenth.

In another instance a woman was admitted to the hospital (March 7) suffering from colonic obstruction. Only two counts of red cells were made: one three days prior to, and another four days after the operation (chart 3). The heavy solid line, March 8 to 15, indicates the degree of

concentration. However, the heavy broken line is the more probable curve, since there was no reason for an increased cell count prior to the operation (March 11). In this instance the concentration of the blood gave warning of circulatory deficiency four days before the blood pressure began its final decline.

In another case, rectal resection for carcinoma, hemoconcentration of 40 per cent occurred within a few hours, while the blood pressure was at its highest recorded point (chart 4). Transfusion of blood and repeated

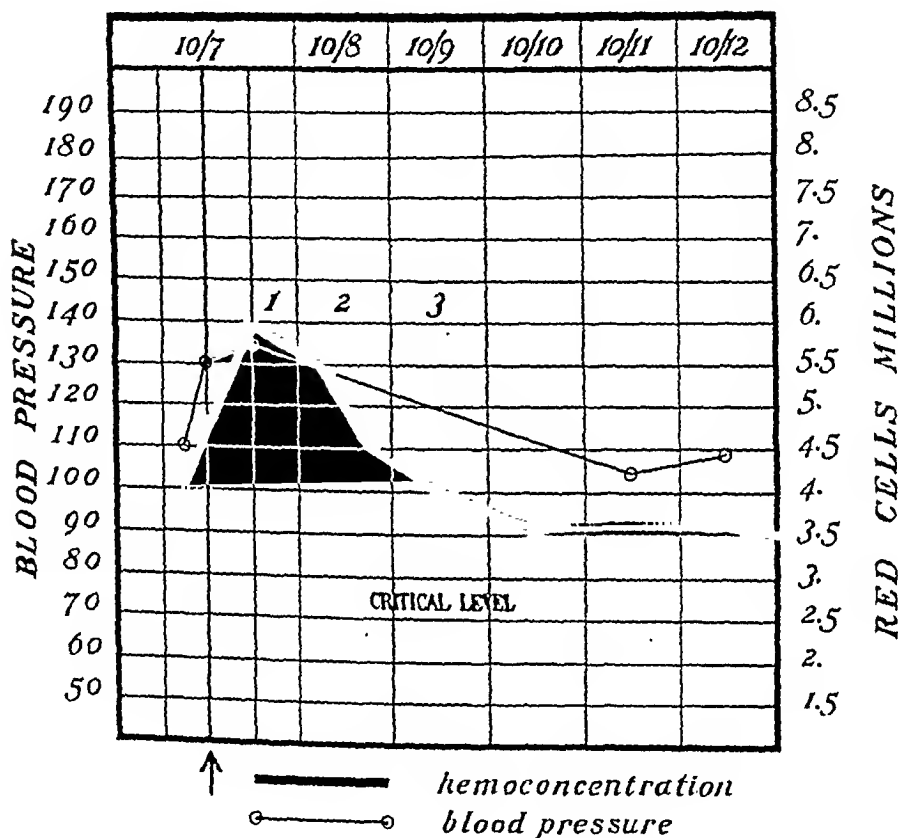


CHART 4. Curves of hemoconcentration and blood pressure after operation (rectal resection for carcinoma, arrow) followed by recovery. Note the immediate rise in concentration indicating the imminence of circulatory failure, and the accompanying rise in arterial pressure indicating active compensation. Transfusion of blood and glucose-saline solution intravenously were given after the operation and on the next day (1 and 2). Saline hypodermoclysis was given on the following day (3).

intravenous infusions of glucose-saline solution after the operation and on subsequent days were followed by recovery.

Circulatory failure incident to systemic intoxication was illustrated by an instance of icterus gravis, with fatal termination on the sixth day of hospitalization. The blood count on May 28, the day after admission, was 4,490,000. Two days later it had risen to 6,240,000—an increase of 40 per cent. During this time the blood pressure rose from 110 to 130 mm. of mercury. Two days later the blood pressure had declined only to 120 but

the decline continued precipitately, ending in death (chart 5). Hemoconcentration in this instance preceded the circulatory collapse by two days, during which time the blood pressure gave no intimation of impending failure of compensation.

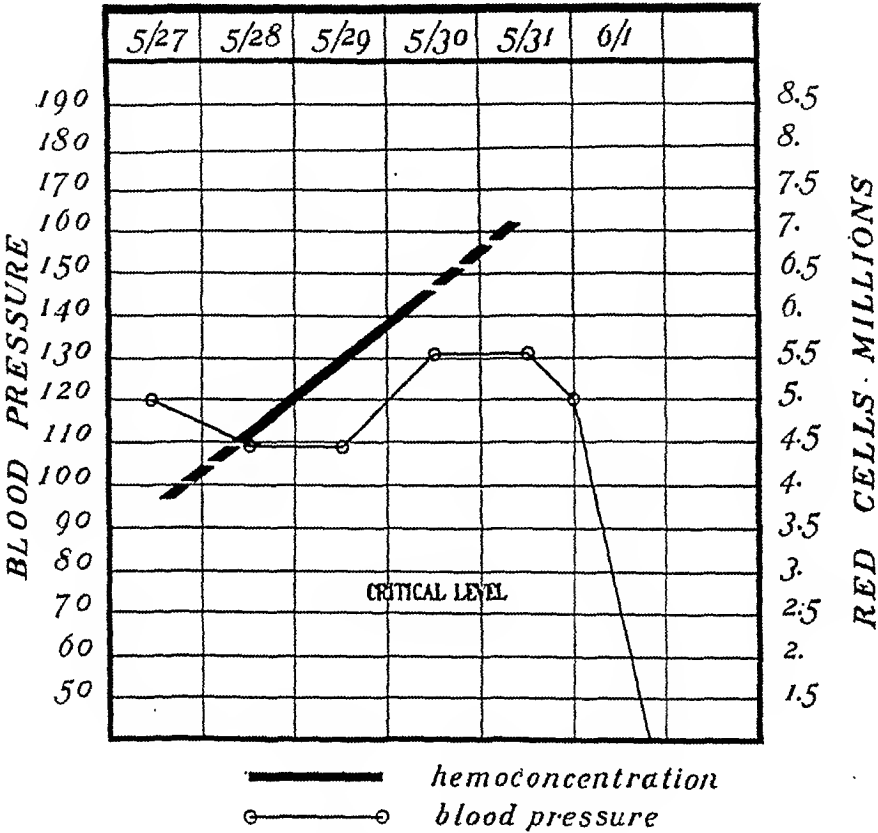


CHART 5. Curves of hemoconcentration and blood pressure during circulatory failure incident to icterus gravis. Time is shown in calendar days. Only two counts of erythrocytes were made. The heavy solid line connects them. In this instance hemoconcentration of 40 per cent was accompanied by a compensatory rise in arterial pressure, and occurred two days before death. Note the precipitate fall in blood pressure when compensation failed.

I have performed or supervised numerous experiments in which data on the hemoglobin and red cell content of the blood were obtained with scrupulous care. Hemoconcentration was used in several series as a criterion of the development and of the degree of shock produced experimentally. In other series the effects of various substances upon the concentration of the blood and upon the circulation were studied. Many of the results have been published and some await publication. The features of these experiments which bear upon the significance of hemoconcentration will be summarized briefly.

The experiments included: finely ground normal tissues, such as muscle, liver, kidney and others, introduced intraperitoneally; watery extracts and autolysates of normal tissues given intravenously or intraperitoneally; bile and its salts, peptone, bacterial cultures and toxins, histamine, moccasin

and rattlesnake venoms and emetin injected intravenously or intraperitoneally; barbiturates given by mouth or by injection; burns, trauma to muscles, intestinal manipulation and strangulation produced under ether anesthesia; and the effects of normal horse serum in sensitized animals.

Such experiments were done on 147 dogs, 98 guinea pigs, 36 cats and on smaller numbers of rabbits, rats and monkeys. Regularly and without exception, the agents and conditions mentioned produced hemoconcentration in each animal and species. This appeared immediately and its degree was proportional to the apparent severity of the accompanying illness.

When recovery followed, the blood returned to its normal corpuscular composition. When death resulted, the postmortem findings regularly showed evidence of capillary damage in visceral areas. This evidence included serous effusions, dilatation of capillaries and venules with apparent stasis of blood in them, ecchymoses and edema in various tissues. The edema fluid was shown to have a high protein content.

The evidence summarized from published reports indicates that acute erythrocytosis is etiologically related to the mechanism by which circulatory failure or collapse develops in a wide variety of clinical conditions. Most authors attributed this directly to the leakage of fluid through endothelium which has been rendered abnormally permeable by injury. Landis' studies on capillary phenomena indicate that any agent or condition injurious to capillaries increases the permeability of the endothelium.

The experiments and clinical observations which I have recorded furnish direct support and confirmation for the interpretations just given. Landis stated that the development of capillary stasis, seen in living tissues, is the surest sign of endothelial permeability. It may be stated with equal assurance that *hemoconcentration is the surest and earliest clinical sign of endothelial permeability* sufficient in degree or extent to affect the efficiency of the systemic circulation.

It is strange that a phenomenon which is so grave in its import, so common in its occurrence and so easily demonstrated, has not been utilized by physicians in their clinical study of patients.

SUMMARY

Reported observations on hemoconcentration indicate that this phenomenon occurs rather frequently in grave conditions of disease quite diverse in origin. Undoubtedly this survey is far from complete, but the number of instances found is sufficiently large and diversified to justify a summary of the authors' observations and interpretations.

It appears that hemoconcentration is regularly associated with a type of circulatory deficiency in which loss of plasma volume is the essential feature.

The loss of fluid may result either from endothelial damage which allows for leakage of plasma into the tissue spaces, or from dehydration incident to vomiting, diarrhea and perspiration.

This loss may be compensated in part by absorption of fluid from the tissues and in part by constriction of the vascular walls, especially the heart, arteries and spleen and, to a lesser degree, by constriction of the veins and capillaries.

So long as the mechanism of compensation is effective, no marked deficiency is evident. When compensation becomes inadequate, the blood pressure declines progressively, anoxia develops and the syndrome of shock is manifested.

So long as the vascular endothelium is able to perform its part in the maintenance of fluid balance, there is dehydration of the tissues but not of the blood. In advanced stages of shock the vascular system is neither able to absorb nor to retain fluid. It appears that the critical point in this mechanism is the physiologic state of the vascular endothelium.

This type of circulatory deficiency may develop whenever and however the capillaries in an extensive visceral area are rendered atonic.

A rising curve of concentration is as ominous as a falling curve of arterial pressure. But the former occurs early and indicates the developmental stage of circulatory deficiency while the latter indicates the failure of compensation and the imminence of death.

Circulatory failure in its *incipient* stage may be recognized by the presence of hemoconcentration. This feature is of inestimable practical value, for treatment must be applied early, otherwise it will be ineffective.

REFERENCES

- ADAIR, F. L., and STIEGLITZ, E. J.: Obstetrical medicine, 1934, Lea and Febiger, Philadelphia.
- ALLEN, F. M.: Physical and toxic factors in shock, Arch. Surg., 1939, xxxviii, 155.
- ANDREWS, A., HARKINS, H. N., HARMON, P. H., and HUDSON, J.: Shock from bile injections, Ann. Surg., 1937, cv, 392.
- BAINBRIDGE, F. A., and BULLEN, H. B.: The hemoglobin value of the blood in surgical shock, Lancet, 1917, ii, 51.
- BAINBRIDGE, F. A., and TREVAN, J. W.: Epinephrine shock, Brit. Med. Jr., 1917, i, 381.
- BARADUC, H.: Union Méd., 1863, xviii, 321.
- BARDEEN, C. R.: On certain visceral pathological alterations the result of superficial burns, Bull. Johns Hopkins Hosp., 1896-97, vii, 81; Jr. Exper. Med., 1897, ii, 501.
- BARNARD, H. L.: Intestinal obstruction in Allbutt's System of Medicine, 1907, iii, 718.
- BAYLISS, W. M., and CANNON, W. B.: Note on muscle injury in relation to shock, Sp. Rept. No. 26, p. 19.
- BAZETT, H. C.: Macleod's Physiology in Modern Medicine, 1938, Mosby, St. Louis, ed. 8, 429-442.
- BAZETT, M. C.: Value of hemorrhage and blood pressure observations in surgical cases, Sp. Rept. No. 25; 181.
- BECKY, K., and SCHMITZ, E.: Klinische und chemische Beiträge zur Pathologie der Verbrennung, Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1919, xxxi, 416.
- BLACK, J. H., and KEMP, H. A.: Blood density in anaphylaxis and in hay fever, Am. Jr. Clin. Path., 1937, vii, 300.
- BLALOCK, A., and ASSOCIATES: Experimental shock, Arch. Surg., 1931, xxii, 598, 611, 617.
- BRODIE, T. G.: Physiologic action of diphtheria toxin, Brit. Med. Jr., 1899, ii, 1282.
- CANNON, W. B., FRASER, J., and HOOPER, A. N.: Some alterations in the distribution and character of the blood, Jr. Am. Med. Assoc., 1918, lxx, 526.

- CANTACUZENE: Sur les variations des globles rouges provoquées par les injections de sérum hémolytique, *Ann. de l'Inst. Pasteur*, 1900, xiv, 378.
- COBBETT, L.: Shock and collapse, *Allbutt's System of Med.*, 1897, ii, 320.
- COHN, E.: Veränderung d. Hämoglobin sowie d. Eiweissgehaltes bei Muskelarbeit und Schwitzen, *Ztschr. f. Biol.*, 1919-20, lxx, 366.
- COONSE, G. K., FOISE, P. S., ROBERTSON, H. F., and AUFRANC, O. E.: Traumatic and hemorrhagic shock, *New Eng. Jr. Med.*, 1935, ccxii, 647.
- COPE, ZACHARY: Clinical research in acute abdominal disease, 1927, xii, 164-206, Oxford University Press, London. A criticism of current views of shock and collapse, *Proc. Roy. Soc. Med.*, 1928, xxi, 599.
- CRILE, GEO. W.: Hemorrhage and transfusion, New York, 1909, p. 75.
- CROWELL, B. C.: Notes on the diagnosis of Asiatic cholera at autopsy, *Philippine Jr. Sci.*, 1914, ix, 361.
- DALE, H. H., LAIDLAW, P. P., and RICHARDS, A. N.: The action of histamine: its bearing on traumatic toxemia as a factor in shock, *Spec. Rept. Series No. 26:8*.
- DAVIS, J. E.: Cobalt polycythemia in the dog, *Proc. Soc. Exper. Biol. and Med.*, 1937, xxxvii, 96.
- DEAN, H. R., and WEBB, R. A.: Morbid anatomy of anaphylactic shock in dogs, *Jr. Path. and Bact.*, 1924, xxvii, 51, 65, 79.
- DE LEE, J. B.: Principles and practice of obstetrics, 1933, 6th ed., p. 392, W. B. Saunders, Philadelphia.
- DEAVER, J. B.: A clinical study of pancreatitis, *Med. Jr. and Rec.*, 1924, exix, 129.
- DETAKATS, G., and MACKENZIE, M. B.: Acute pancreatic necrosis and its sequelae; a critical study of 30 cases, *Ann. Surg.*, 1932, xcvi, 418.
- EBBECKE, U.: Die lokale vasomotorische Reaktion der Haut und der inneren Organen, *Arch. f. d. ges. Physiol.*, 1917, clxix, 1. Die lokale galvanische Reaktion der Haut, *Ibid.*, 1921, clxxxix, 230. Capillarerweiterung, Urticaria und Schock, *Klin. Wehnschr.*, 1923, ii, 1725.
- EDMONDS, C. W., and NELSON, E. E.: Polycythemia by injections of epinephrine, *Jr. Exper. Med.*, 1925, xli, 1.
- EPPINGER, H.: Über Kollapszustände, *Wien. klin. Wehnschr.*, 1934, xlvii, 10, 47.
- EPPINGER, H., and SCHURMEYER, K.: Über den Kollaps und analoge Zustände, *Klin. Wehnschr.*, 1928, vii, 777.
- EPPINGER, H., KAUNITZ, H., and POPPER, H.: Die seröse Entzündung, 1935, Springer, Berlin.
- ERLANGER, GESELL, R., GASSER, H. S., and ELLIOTT, B. L.: An experimental study on surgical shock, *Jr. Am. Med. Assoc.*, 1917, lxi, 2089.
- FREEMAN, N. E.: Decrease in blood volume after prolonged hyperactivity of the sympathetic nervous system, *Am. Jr. Physiol.*, 1933, ciii, 185.
- FREEMAN, N. E., SHAW, J. L., and SNYDER, J. C.: Peripheral blood flow in surgical shock, *Jr. Clin. Invest.*, 1935, xv, 651.
- ESSEX, H. E., and MARKOWITZ, J.: The physiologic action of rattlesnake venom, *Am. Jr. Physiol.*, 1930, xcii, 317 et seq.
- GIESBOCK, F.: Die praktische Bedeutung der Blutdruckmessung, *Deutsch. Arch. f. klin. Med.*, 1905, lxxxiii, 363.
- HAMILTON, A.: Industrial poisons in the United States, 1925, Macmillan, New York.
- HANZLIK, P. J., and TANTER, M. L.: Experimental edema of the head and neck, *Jr. Lab. and Clin. Med.*, 1923-24, ix, 166.
- HARDING, M. E.: The circulatory failure of diphtheria, 1919, U. of London Press, London. The toxemic stage of diphtheria, *Lancet*, 1921, i, 737.
- HARKINS, H. N.: Experimental burns, *Arch. Surg.*, 1935, xxxi, 71. Mesenteric vascular occlusion, *Arch. Path.*, 1936, xxii, 637.
- HARKINS, H. N., and HARMON, P. H.: Plasma exudation, *Ann. Surg.*, 1937, cvi, 1070.
- HARMON, P. H., and HARKINS, H. N.: Peritonitis, *Arch. Surg.*, 1937, xxxiv, 580.
- HARROP, G. A.: Polycythemia, *Medicine*, 1928, vii, 291.

- HENDERSON, YANDELL: Failure of circulation, *Am. Jr. Physiol.*, 1910, xxvi, 260.
- HUNT, E. H.: The regulation of body temperature in extremes of dry heat, *Jr. Hyg.*, 1912, xii, 479.
- HUNTER, WM.: A method of raising the specific gravity of the blood, *Jr. Physiol.*, 1890, xi, 115.
- V. JAKSCH, R.: Beitrag zur Kenntnis der acuten Phosphorvergiftung des Menschen, *Deutsch. med. Wchnschr.*, 1893, xix, 10.
- KELLAWAY, C. H.: The vaso-depressant action of venom of Australian copperhead, *Australian Jr. Exper. Biol. and Med. Sci.*, 1936, xiv, 57.
- KEITH, N. M.: Blood volume in wound shock, *Sp. Rept. Series No. 26*, xxxvi, No. 27:3.
- KILGORE, E. S.: Polycythemia in a feather-dyer, *Jr. Am. Med. Assoc.*, 1927, lxxxix, 342.
- KING, H. M.: Post-operative non-septic leukocytosis and other blood conditions, *Am. Jr. Med. Sci.*, 1902, cxxiv, 450.
- KOPP, I., and SOLOMON, H. C.: The shock syndrome in therapeutic hyperpyrexia, *Arch. Int. Med.*, 1937, lx, 597.
- KROGH, AUGUST: Anatomy and physiology of the capillaries, 2nd ed., 1929, Yale Univ. Press, New Haven.
- LAMSON, P. D.: Red corpuscle concentration in acute physiological conditions, *Jr. Pharm. and Exper. Therap.*, 1920, xvi, 125.
- LANDIS, E. M.: Capillary pressure and capillary permeability, *Physiol. Rev.*, 1934, xiv, 404. Passage of fluid through the capillary wall, *Am. Jr. Med. Sci.*, 1937, cxci, 297.
- LEWIS, THOMAS: Blood vessels of the human skin and their responses, 1927, Shaw and Sons, London.
- LIPSITZ, S., FUERTH, A. L., and CROSS, A. T.: Polycythemia induced by tincture of cantharides, *Arch. Int. Med.*, 1917, xx, 889, 913.
- LOCKE, E. A.: Blood examination in 10 cases of severe burns, *Boston Med. and Surg. Jr.*, 1902, cxlvii, 480.
- MACCALLUM, W. G.: Mechanism of circulatory failure in diphtheria, *Am. Jr. Med. Sci.*, 1914, cxlviii, 38.
- MANN, F. C.: The peripheral origin of surgical shock, *Bull. Johns Hopkins Hosp.*, 1914, xxv, 205.
- MANWARING, W. H., CHILCOTE, R. C., and HOSEPIAN, V. M.: Capillary permeability in anaphylaxis, *Jr. Am. Med. Assoc.*, 1923, lxxx, 303.
- MASON, E. C., and DAVIDSON, E. C.: A study of tissue autolysis in vivo, *Jr. Lab. and Clin. Med.*, 1925, x, 622.
- MASON, E. C., and LEMON, C. W.: Autointoxication and shock, *Surg., Gynec. and Obst.*, 1931, lxi, 60.
- MOON, VIRGIL H.: (1) Shock and related capillary phenomena, 1938, Oxford University Press, New York. (2) Shock, its mechanism and pathology, *Arch. Path.*, 1937, xxiv, 642 and 794. (3) The shock syndrome in medicine and surgery, *ANN. INT. MED.*, 1935, viii, 1633-1644.
- MOON, V. H., and KENNEDY, P. J.: Changes in blood concentration incident to shock, *Jr. Lab. and Clin. Med.*, 1933, xix, 295.
- MOON, V. H., and MORGAN, D. R.: Shock, the mechanism of death following intestinal obstruction, *Arch. Surg.*, 1936, xxxii, 776. Experimental pulmonary edema, *Arch. Path.*, 1936, xxi, 565.
- MOORE, J. E.: Modern treatment of syphilis, 1933, Thomas, Springfield, Ill.
- MORGULIS, S., and MUIRHEAD, A. L.: The physiologic action of cantharis, *Arch. Int. Med.*, 1919, xxiii, 190.
- PACK, G. T.: The pathology of burns, *Arch. Path.*, 1926, i, 767.
- ROGERS, LEONARD: Cholera and its treatment, 1911, Oxford Univ. Press, London.
- ROGOFF, J. M., and STEWART, G. N.: Studies on adrenal insufficiency in dogs, *Am. Jr. Physiol.*, 1926, lxxviii, 683; 1928, lxxxiv, 649.

- ROMBERG, E. and PÄSSLER, H.: Untersuchungen über die allgemeine Pathologie und Therapie der Kreislaufstörung bei acuten Infektionskrankheiten, *Deutsch. Arch. f. klin. Med.*, 1899, lxiv, 652.
- RÖSSLE, R.: Hepatöse und Hepatitis, *Schweiz. med. Wchnschr.*, 1929, lix, 4.
- ROWNTREE, L. G.: Addison's disease, *Jr. Am. Med. Assoc.*, 1925, lxxxiv, 327.
- SCHJERNING, O.: Über den Tod in Folge von Verbrennung, *Vrtljrschr. f. gericht. Med.*, 1884, xl, suppl. 24-66.
- SCUDDER, J., ZWEMER, R. L., and TRUSZKOWSKI, R.: Potassium in acute intestinal obstruction, *Surgery*, 1937, i, 74.
- SCUDDER, J., ZWEMER, R. L., and WHIPPLE, A. O.: Acute intestinal obstruction, *Ann. Surg.*, 1938, cvii, 161.
- SEEGAL, B. C.: Agents of disease and host resistance, 1935, Thomas, Baltimore, Chapter VI.
- SEELY, S. F., ESSEX, H. E., and MANN, F. C.: Comparative studies on shock under ether and under sodium amylal anesthesia, *Ann. Surg.*, 1936, civ, 332.
- SILBERMANN, R.: Ein Beitrag zur Polycythämie bei Phosphorvergiftung, *Prag. med. Wchnschr.*, 1907, xxxii, 167.
- SIMONDS, J. P.: Relation between blood volume and blood pressure in anaphylactic and peptone shock, *Am. Jr. Physiol.*, 1925, lxxii, 1.
- SIMONART, A.: Étude expérimentale sur la toxémie traumatique et la toxémie des grands brûlés, *Arch. Internat. Pharmacodyn. Therap.*, 1930, xxxvii, 269.
- SHERRINGTON, C. S., and COPEMAN, S. M.: Experimental variations in specific gravity of the blood, *Jr. Physiol.*, 1893, xiv, 83.
- SOLLMANN, T.: Manual of pharmacology, Ed. 5, 1936, W. B. Saunders, Philadelphia, pp. 149, 150, 927, 928.
- SWINGLE, W. W., PFIFFNER, J. J., VARS, H. M., BOTT, P. A., and PARKINS, W. M.: The function of the adrenal cortical hormone and the cause of death from adrenal insufficiency, *Science*, 1933, lxxvii, 58.
- TAPPEINER: Veränderungen d. Blutes u. d. Muskeln nach ausgedehnten Hautverbrennungen, *Centralbl. f. d. med. Wissensch.*, 1881, xix, 385.
- TAUSSIG, O.: Blutbefunde bei acuter Phosphorvergiftung, *Arch. f. exper. Path.*, 1892, xxx, 161.
- UNDERHILL, F. P.: The lethal war gases, *Arch. Int. Med.*, 1939, xxiii, 753.
- UNDERHILL, F. P., CARRINGTON, G. L., KAPSINOW, R., and PACK, G. T.: Blood concentration changes in extensive superficial burns, *Arch. Int. Med.*, 1923, xxxii, 31.
- UNDERHILL, F. P., and RINGER, M.: Blood concentration changes in influenza, *Jr. Am. Med. Assoc.*, 1920, lxxv, 1531.
- UNDERHILL, F. P., and RINGER, M.: Relation of blood concentration to peptone shock, *Jr. Pharm. and Exper. Therap.*, 1922, xix, 135.
- VALE, F. P.: Concentration of the blood, *Med. Rec.*, 1904, lxvi, 325.
- WALTHER, W. W.: Blood changes after surgical shock, *Lancet*, 1937, i, 6.
- WEBER, F. P.: Polycythemia, erythrocytosis and erythremia, 1921, Lewis & Co., London.
- WILMS, M.: *Mittel. a. d. Grenzgeb. d. Med. u. Chir.*, 1901, viii, 393.
- WILSON, W. C., ROWLEY, G. D., and GRAY, N. A.: Acute toxemia of burns, *Lancet*, 1936, i, 1400.
- WILSON, W. C., MACGREGOR, A. R., and STEWART, C. P.: Burns under modern treatment, *Brit. Jr. Surg.*, 1938, xxv, 826.
- WINTERS, C. A., and HARTMAN, F. A.: Water balance in adrenal insufficiency, *Proc. Soc. Exper. Biol. and Med.*, 1934, xxxii, 542.
- ZWEMER, R. L., and SCUDDER, J.: Blood potassium during experimental shock, *Surgery*, 1938, iv, 510.

BACTERIOLOGY OF ENDOCARDITIS WITH REPORT OF TWO UNUSUAL CASES *

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SINCE 1900, every review ^{1, 2, 3, 4, 5} of the exciting causes of bacterial endocarditis has always included the *Streptococcus hemolyticus* and *mitior*, *Diplococcus pneumoniae*, the *Hemophilus influenzae*, the *Staphylococcus aureus* and the *Neisseria gonorrhoeae*. These organisms no longer arouse comment when found. However, it is still unusual to see cases due to other bacteria and this report concerns itself mainly with the rarer forms of bacterial endocarditis.

A review of the literature reveals reports of many isolated cases of endocarditis due to organisms ordinarily considered non-pathogenic, some of cases due to organisms pathogenic for man but rarely involving the heart, and finally, a few cases caused by organisms which defy classification. These observations are not new, for Horder ² in 1909 noted that "micro-organisms difficult to classify are not seldom obtained from cases of endocarditis even during life." It is still true, however, that when compared with the common causative bacteria the incidence of the rarer forms is extremely low. Yet one cannot agree with Blumer ⁵ who states that "so few other organisms have been described during the era of modern clinical bacteriology that we are constrained to believe that some, at least, of the older observations concern accidental contamination or terminal invaders rather than the true cause of the disease." Careful bacteriological investigations in any active clinical laboratory not infrequently isolate unclassified organisms as causative factors in different types of infections.

Many organisms have been described in the literature. Only those cases with careful antemortem and postmortem bacteriological studies have been included. No attempt has been made to record the innumerable varieties of streptococci reported. Organisms which have been described include the following:

- Streptococceae—*Streptococcus mitior*
Streptococcus pyogenes
Diplococcus pneumoniae ⁶
- Neisseriae—*Neisseria gonorrhoeae* ⁷
Neisseria intracellularis ⁸
Neisseria catarrhalis ⁹
Neisseria sicca ^{10, 11, 12}
Neisseria flava ¹³

* Received for publication December 1936.

This investigation was carried out at the Pathological Laboratories of the Boston City Hospital in 1931-1932. Thesis presented as partial requirement for the degree of Doctor of Medical Science, Columbia University, 1935.

- Hemophileae—*Hemophilus influenzae* ¹⁴
Hemophilus hemolyticus ¹⁵
- Micrococceae—*Staphylococcus aureus*
Staphylococcus albus ²
Gaffkya tetragena ⁵
- Bacteriaceae—*Escherichia coli* ^{1, 2}
Escherichia acidilactici ¹⁶
Eberthella typhi ¹⁷
Aerobacter aerogenes ²
- Miscellaneous—*Pseudomonas aeruginosa* ^{1, 4}
Bacillus anthracis ¹⁸
Corynebacterium pseudodiphthericum ¹⁹
Actinomyces hominis ²⁰
Brucella melitensis ²¹
Pasteurella pestis ²²
Micrococcus endocarditis rugatus ^{23, 24}
Unclassified gram negative coccus ²⁵
Mycobacterium tuberculosis ²⁹

Some of the rarer organisms mentioned above produced clinical syndromes suggesting acute bacterial endocarditis while others gave rise to the subacute variety. Likewise from autopsy reports, it was apparent that focal glomerular lesions were found in a considerable number of the cases. Both normal and previously damaged valves have been affected by these organisms.

While working in the Pathological Laboratory at the Boston City Hospital, the author had the opportunity to study intensively the antemortem and postmortem bacteriology, pathology and serology of two cases of endocarditis due to unusual organisms. The protocols and bacteriological investigations, together with clinical abstracts, follow.

CASE REPORT

Clinical History: The patient was a 26-year-old white male who entered the hospital in March 1932 complaining of frequent chills of six weeks' duration. One week before admission, when looking for a job, the patient was told that he had a heart murmur. No history of rheumatic fever could be obtained.

Family history and past history were irrelevant.

Physical Examination: The heart was not enlarged. At the apex there was a faint systolic thrill and a harsh rough systolic murmur transmitted to the axilla. The blood pressure was 100 mm. of mercury systolic and 60 mm. diastolic. The spleen was not palpable. The nails were moderately curved.

Laboratory Findings: The urine was normal save for red cells on several occasions. The white blood count ranged around 16,000. Many blood cultures revealed a gram negative diplococcus.

Course: The temperature ranged between 101° F. and 103° F. with corresponding elevation in pulse. The patient had frequent chills followed by profuse sweating

in the evening. On March 18, the patient had sudden pain in the right arm, following which radial and brachial artery pulsations were absent. Ten days later a similar episode involved the right leg. There were numerous abdominal pains suggesting splenic and renal infarcts. At this time, râles were heard throughout the chest. A roentgen-ray was interpreted as revealing bronchopneumonia or metastatic abscesses. The patient became progressively paler and developed a café-au-lait color. Dyspnea increased and became very marked terminally. The patient died seven weeks after admission.

AUTOPSY

An autopsy was performed April 22, one and a half hours post mortem. The positive findings were as follows:

There is moderate clubbing of the fingers and toes.

The pleural and pericardial cavities contain 200 c.c. and 100 c.c. respectively of clear rusty brown fluid.

Heart: Weight 350 grams. The myocardium and endocardium are essentially negative. The pulmonary, tricuspid, and aortic valves are normal. The free edge of practically the entire anterior leaflet of the mitral valve is eroded and is covered with clusters of large, irregular, friable vegetations. These are also attached to ruptured *chordae tendineae*. The uninvolved portions of the mitral valve are normal in appearance and their *chordae tendineae* thin and delicate. Microscopically the vegetations consist of irregular bands of fresh and hyalinized fibrin in which are clumps of diplococci. These are gram negative when stained by the MacCallum-Goodpasture technic.

Lungs: Both lungs feel firm, resilient and rubbery with a definite diffuse increase in fibrous tissue, more marked at the apices. The sections show a well advanced organizing bronchopneumonia.

Spleen: Weight 200 grams; it is soft and shows large septic infarcts which are soft, yellow, and almost purulent in character. There are also several small healed infarcts.

Liver: Weight 1700 grams. Lobulations are distinct and in places lobules are yellowish gray in appearance. Microscopically the central zone of every lobule involving up to five-sixths of the entire lobule, is necrotic and shows invasion by many leukocytes.

Kidneys: Weight 380 grams. Several small infarcts are noted. Microscopically only one focal glomerular lesion could be found in the four sections studied. Otherwise the sections are not remarkable.

Brain: There is a slight extravasation of blood in the subarachnoid space covering the left occipital lobe.

Vascular System: There is a mycotic aneurysm of the superior mesenteric artery about 3 cm. from its origin. The aneurysmal portion measures about 2 cm. in diameter and is filled with an adherent laminated thrombus. One of the branches, distal to the aneurysm, is filled with greenish pus. Sections show almost complete disappearance of the intima and media, the wall of the aneurysm being made up of a thin layer of necrotic intima and media containing many polymorphonuclear leukocytes and fibrin.

Anatomic Diagnosis: "Acute endocarditis; organizing bronchopneumonia; septic infarcts of spleen; central necrosis of liver; infarcts of kidney; mycotic aneurysm of superior mesenteric artery; subarachnoid hemorrhage."

BACTERIOLOGY

Five of six antemortem blood cultures revealed a gram negative bean-shaped diplococcus. Growth was noted after about 48 hours incubation. At the time of autopsy, smears taken from the vegetations, from the septic splenic infarct and

from the suppurative mycotic aneurysm of the superior mesenteric artery revealed a gram negative diplococcus. Three cultures of heart's blood taken post mortem, one about 15 minutes after death, remained sterile but pure cultures were obtained from the lesions noted above. MacCallum-Goodpasture bacterial stains on sections of the vegetations revealed the clumps of organisms to be gram negative with quite a few gram positive organisms of similar morphology scattered through them.

Morphology and Cultural Characteristics: The organism was a small, non-motile, gram negative, biscuit-shaped diplococcus arranged quite often in tetrads and frequently in dense clumps. It varied considerably in size and staining reactions. It grew best on ascitic agar giving rise to round, grayish-white, glistening, smooth, convex colonies with an average diameter of 0.5 mm. The colonies were slightly mucoid, tenacious and adherent to the medium. The microscope showed slight wrinkling of the central portion of the colonies with the periphery perfectly smooth. Only after repeated subculturing on ascitic agar did the organisms grow at room temperature or on plain agar. It did not produce pigment on ascitic agar, blood agar, plain agar and Loeffler's serum medium. In blood broth, it formed a diffuse cloud with a coarsely granular sediment. It was difficult to emulsify and was auto-agglutinable when suspended in saline. It grew slightly under strictly anaerobic conditions.

Fermentation Reactions: These were tested in ascitic peptone broth, containing Andrade's indicator and 1 per cent sugars. Several tests were done with consistent results. Dextrose, saccharose, maltose, levulose, and raffinose were fermented while no change in reaction was noted in lactose and galactose. Final readings were made 14 days after the inoculation of the sugars.

Variability: Cultures were still alive after *seven* days in the icebox and *ten* days in the incubator. Heating for 30 minutes at 55° C. killed the organisms.

Pathogenicity: Heavy saline suspensions of recently isolated cultures were non-pathogenic for mice and guinea pigs when injected intra-peritoneally.

SEROLOGY

It was impossible to do agglutination tests with this organism because it agglutinated spontaneously in saline. This made it necessary to do precipitin tests. In all the tests outlined below a carbolized antigen of the various organisms was used. Heavy suspensions of the organisms in 0.5 per cent phenol were incubated for one week at 37.5° C. The suspensions were shaken daily and at the end of one week were centrifuged at high speed. The clear supernatant fluid was pipetted off and made up to 0.9 per cent saline. ("Neisseria pharyngis antigen" refers to the antigen made from the organism isolated from the patient.)

Type 1 *Neisseria intracellularis* obtained from the Commonwealth of Massachusetts Antitoxin and Vaccine Laboratory was used in making up the meningococcus antigen.

The gonococcus used was obtained from the urethra of a patient with chronic gonorrheal urethritis.

In the complement fixation test the serum used was obtained from the patient about one week before death.

In the other tests the serum used was obtained by cardiac puncture just after death and at time of autopsy, one and a half hours post mortem. The polyvalent antimeningococcus serum was obtained from the Commonwealth of Massachusetts Antitoxin and Vaccine Laboratory and the antigonococci serum was obtained from Parke, Davis and Company.

An antiserum was obtained by immunizing a rabbit over a period of six weeks with increasing doses of the organisms. The last dose consisted of living organisms made up of saline washings of the 24 hour growth of four ascitic agar slants injected intravenously. The serum obtained had a precipitin titer of 1-1280 with the carbolized antigen of the organism.

The *Pharyngis siccus* was kindly supplied by Dr. C. W. Rake of the Rockefeller Institute for Medical Research.

The polyvalent gonococcus antigen was obtained from the Commonwealth of Massachusetts Wassermann Laboratory.

AGGLUTINATION

The four known types of meningococci were used in an agglutination test with the *Neisseria pharyngis* antiserum. The results were negative throughout.

COMPLEMENT FIXATION

The complement fixation tests were done with one-fourth the quantities employed in the Wassermann test, using 0.5 c.c. of sensitized sheep cells and two units of complement. In each test, patient's antemortem serum was used in the following quantities: 0.1 c.c., 0.05 c.c., 0.037 c.c., 0.025 c.c., 0.013 c.c., 0.005 c.c. The Roman numerals indicate the different tests:

CHART I
COMPLEMENT-FIXATION TESTS
Neisseria pharyngis Antigen

I	++++	++++	++++	++++	+++	±
II	++++	++++	++++	++++	+	±
III	+++	+++	+++	+++	±	-
IV	-	±	-	-	-	-
Anticomplementary control	-	-	-	-	-	-

Meningococcus Antigen

I	+++	++	+	±	-	-
II	++	+	±	-	-	-
III	++	±	-	-	-	-
IV	+	-	-	-	-	-
Anticomplementary control	-	-	-	-	-	-

Gonococcus Antigen

I	+	+	±	-	-	-
II	+	±	-	-	-	-
III	+	±	-	-	-	-
IV	-	-	-	-	-	-
Anticomplementary control	-	-	-	-	-	-

In I, 0.05 c.c. of antigen was used throughout with the varying amounts of serum as mentioned above; in II, 0.025 c.c. of antigen; in III, 0.012 c.c. of antigen; in IV, 0.005 c.c. of antigen.

An anticomplementary control was set up similar to I in every condition except for the omission of the antigen.

PRECIPITIN TESTS

To test the strength of the various antigens and sera used, the following precipitin tests were done. Undiluted sera were used in all the tests and the titers mentioned refer to dilution of the antigen:

I. *Meningococcus* Antigen and *Antimeningococcus* serum.

This was positive up to 1-160 with \pm at 1-320.

II. *Gonococcus* Antigen and *Antigonococcus* serum.

This was positive up to 1-160 with \pm at 1-320.

III. *Meningococcus* Antigen and *Antigonococcus* serum.

This was positive up to 1-20.

IV. *Gonococcus* Antigen and *Antimeningococcus* serum.

This was positive up to 1-80.

PRECIPITIN TESTS WITH PATIENT'S POSTMORTEM SERUM

These were done using the various antigens. With the *Neisseria pharyngis* antigen a zone phenomenon was observed. The final titer was 1-160 with \pm at 1:200. With the *Neisseria intracellularis* antigen the final titer was 1-20, with the *Neisseria sicca* antigen 1-10, while none was obtained with the *Neisseria gonorrhoeae* antigen.

CHART II

Precipitin Tests with Patient's Postmortem Serum

Antigen	Final Dilutions of Antigens							Saline	Normal Patient's Serum
	1:10	1:20	1:40	1:80	1:160	1:200	1:250		
<i>Neisseria pharyngis</i> Antigen	-	-	+	+	+	\pm	-	-	-
<i>N. intracellularis</i> Antigen	+	+	-	-	-	-	-	-	-
<i>N. gonorrhoeae</i> Antigen	-	-	-	-	-	-	-	-	-
<i>N. sicca</i> Antigen	+	-	-	-	-	-	-	-	-

PRECIPITIN TESTS WITH ANTIMENINGOCOCCUS SERUM

Using the *Neisseria pharyngis* antigen a titer of 1-80 was obtained with antimeningococcus.

CHART III

Precipitin Tests with Antimeningococcus Serum

Antigen	Final Dilutions of Antigen							
	1 : 10 :	1 : 20	1 : 40	1 : 80	1 : 160	1 : 200	1 : 250	
<i>Neisseria pharyngis</i> Antigen	+	+	+	+	—	—	—	—

PRECIPITIN TESTS WITH ANTIGONOCOCCUS SERUM

A positive precipitin test was obtained with a dilution of the *Neisseria pharyngis* antigen up to 1-80.

CHART IV

Precipitin Tests with Antigonococcus Serum

Antigen	Final Dilutions of Antigen							Sal- ine
	1 : 10	1 : 20	1 : 40	1 : 80	1 : 160	1 : 200	1 : 250	
<i>Neisseria pharyngis</i> Antigen	+	+	+	+	—	—	—	—

PRECIPITIN TESTS WITH *Neisseria pharyngis* ANTISERUM

The antiserum obtained gave a positive precipitin test with a dilution of the *Neisseria pharyngis* antigen up to 1-1280. However, no positive tests were observed in any dilution of the *N. intracellularis* antigen, the *N. gonorrhoeae* antigen, the *Neisseria pharyngis sicca* antigen and the polyvalent *N. gonorrhoeae* antigen.

DISCUSSION

The morphological, cultural, and serological characteristics of the organism isolated in this case correspond fairly closely to those of the *Neisseria* group of organisms. However, it does not agree specifically with any of the standard strains of gram negative cocci as outlined by Elser and Huntoon.²⁶ It does give the fermentation reactions of *Neisseria sicca*, yet the colony is much smoother and the organisms smaller than the strain of *N. sicca* at our disposal. The investigations of S. P. Wilson²⁷ and G. S. Wilson and Muriel M. Smith²⁸ indicate that the classifications of gram negative cocci on the basis of pigment formation, appearance of colonies and fermentation reactions is very unsatisfactory and that after prolonged cultivation these characteristics may change considerably. They propose that the gram negative cocci of the nasopharynx, apart from the *N. intracellularis*, should be classified under a single group, called *Neisseria pharyngis*. The characteristics of this group are defined and we feel that the organism isolated in this case has most of the characteristics assigned to

the group and should be classified with it. There are only five similar cases reported in the literature; in three the organism involved was *Neisseria sicca*, in one *Neisseria flava* and in one *Neisseria catarrhalis*.

CASE REPORT

Clinical History: The patient was a 25-year old Italian male who considered himself quite well until August 1931 when he developed pains in his extremities. In January 1932, he was first seen in the hospital and presented signs of aortic insufficiency and questionable signs of mitral stenosis. He ran a swinging temperature, had a large spleen and clubbed fingers. A diagnosis of bacterial endocarditis was finally made although only one of several blood cultures showed a gram negative rod which was considered to be a contaminant. At that time he showed no signs of myocardial insufficiency. However, he reentered the hospital in March 1932, complaining of shortness of breath, cough and slight swelling of the ankles.

Physical Examination: The patient appeared ill and was very short of breath. The heart showed tremendous enlargement to the left and some to the right. At the mitral area there were loud presystolic and systolic murmurs, with a to and fro murmur at the base. The liver was enlarged and tender and the spleen was enlarged to percussion. Clubbing of the fingers was quite marked.

Laboratory Findings: The urine on admission showed a slight trace of albumin, 10 red cells and 20 white blood cells per high power field, and a few granular casts. The blood showed a marked secondary anemia; the leukocytes numbered 26,600 per cubic millimeter; polynuclears 89 per cent, lymphocytes 7 per cent and mononuclears 4 per cent.

Course in Hospital: The patient's illness progressed rapidly. He remained very dyspneic and in the last two days became delirious and stuporous. No definite localizing neurological lesions could be demonstrated. The Kahn test was negative. Nonprotein nitrogen was 47 mg. per cent. Blood cultures showed a tiny gram negative diplococcus. The patient died nine days after admission.

AUTOPSY

An autopsy was performed on April 1, three hours postmortem. The positive findings were as follows:

Rigor mortis has not yet set in. The sclerae show a definite icteric tint. There is moderate enlargement of the lymph nodes in the cervical, axillary and inguinal regions. Clubbing of the fingers and toes is quite marked.

Peritoneal, pleural and pericardial cavities contain 100 c.c., 50 c.c., and 50 c.c., respectively, of clear, straw colored fluid.

Heart: Weight 700 grams. The heart is markedly dilated and considerably hypertrophied. There are many tiny ecchymoses beneath the smooth epicardium. Scattered throughout the flabby myocardium are numerous irregular small patches of silvery scarring. The pulmonary and tricuspid valves are essentially negative. The mitral valve is shortened and thickened with its free margin rolled up. The free borders of the leaflet are covered almost completely by a layer of rough, friable vegetations which extend to the endocardium lining the left auricle and also to thickened chordae tendineae, many of which have been ulcerated through leaving their loose ends unattached.

The aortic valve is similarly involved and the cusps, in addition to being eroded, shortened and thickened, are covered along their free borders by vegetations. These are also seen on the intraventricular septum just below the middle aortic cusp. A few endocardial pockets are also seen in this region.

Microscopically the myocardium shows large vascular areas of scarring. The wall of the left auricle is infiltrated with many mononuclears and polymorphonuclears, closely packed in places. Fusing imperceptibly with the underlying endocardium are confluent vegetations made up of an outer shell consisting of masses of organisms plus a few fibrin threads covering a dense collection of polymorphonuclear leukocytes and mononuclears in a network of fibrin. These cells contain numerous intracellular diplococci. The organisms are gram negative when stained by the MacCallum-Goodpasture technic. The aortic and mitral valves are made up of hyalinized connective tissue covered with vegetations similar to those described above.

Lungs: They are boggy and edematous and show a slight terminal bronchopneumonia.

Spleen: Weight 500 grams. It is enlarged and firm and shows a diffuse scattering of irregular, opaque, yellowish-white nodules about 2 mm. in diameter. Microscopically these are infarcts in various stages of organization.

Liver: Weight 2160 grams. Section shows a patchy "nutmeg" appearance. Microscopically one sees a late stage of necrosis involving the central half of practically every lobule.

Kidneys: Weight 600 grams, large and firm. One yellowish-white depressed infarct is noted. In the sections, all the glomeruli show a rather marked increased cellularity and many show focal lesions involving one or more loops.

Brain: In the meninges covering the cortex in the right parieto-occipital region there is a small area of suppuration which extends into the cortex. Microscopically this is made up of a dense collection of polymorphonuclear leukocytes many of which are necrotic.

Lymphoid System: The lymph nodes throughout the body are enlarged and on section appear swollen and edematous. Microscopically the sinuses are distended with numerous large mononuclears which have phagocytosed many polymorphonuclear leukocytes.

Anatomic Diagnoses: Vegetative endocarditis, acute and chronic; sclerosis of myocardium; bronchopneumonia; miliary infarcts of spleen; central necrosis of liver; focal and intracapillary glomerulitis; infarcts of kidney; focal suppurative meningitis; icterus; generalized lymphoid hyperplasia.

BACTERIOLOGY

Four blood cultures out of the eleven taken antemortem were positive for a tiny gram negative diplococcus. Growth was noted only after seven days incubation. At the time of autopsy, smears from the suppurative area in the meninges and from the vegetations on the heart valves, revealed a similar organism. *Streptococcus pyogenes* was recovered from a postmortem blood culture but pure cultures of the gram negative diplococcus were obtained from the vegetations and the meninges. MacCallum-Goodpasture bacterial stains on sections of the vegetations revealed the masses of organisms to be gram negative diplococci although many of the organisms retained the gentian-violet dye.

MORPHOLOGY AND CULTURAL REACTIONS

The organism is a tiny, nonmotile, gram negative diplococcus arranged most often in dense clumps. It is uniform in size but decolorized with some difficulty. There are also a few gram positive diplococci in the dense clumps of gram negative organisms. It grows best on blood agar giving rise to tiny, smooth, raised, milky, glistening colonies after 24 hours incubation at 37° C. Where the growth is heavy there is a slight amount of greenish discoloration to the medium but the organism is not a true methemoglobin former. It does not grow at room temperature, and no

growth occurs on plain agar or on beef infusion broth. It does not produce pigment. In blood broth it gives rise to a fine granular growth with a heavy granular sediment on top of the blood at the bottom of the tube. It reaches its maximum growth on blood agar on about the seventh day. It is difficult to emulsify and is agglutinated spontaneously when suspended in saline. It grows slightly under strictly anaerobic conditions.

Fermentation Reactions: These were tested in ascitic peptone broth containing Andrade's indicator and 1 per cent sugars. These were done on two different occasions with the same results. Dextrose, saccharose and maltose were fermented while no change in reaction was noted with lactose, raffinose, galactose, and levulose. The final readings were made 14 days after the inoculation of the sugars.

Viability: Cultures were still alive after seven days in the icebox and 10 days in the incubator. Heating for 30 minutes at 55° C. killed the organisms.

Pathogenicity: Heavy saline suspensions of the living organisms injected intraperitoneally into mice and guinea pigs were innocuous.

Serology: An antiserum was made by immunizing a rabbit over a period of six weeks with increasing doses of the organism. The last dose consisted of living organisms made up of the saline washings of the 24 hour growth of four blood agar slants injected intravenously. A positive precipitin test was obtained with a dilution of the antigen up to 1-640.

Precipitin tests done with this serum and *Neisseria intracellularis* antigen, the *Neisseria gonorrhoeae* antigen, the polyvalent *Neisseria gonorrhoeae* antigen and the *Neisseria sicca* antigen were all negative. A positive precipitin test was obtained with a dilution of *Neisseria pharyngis* antigen up to 1-20. A precipitin test done with a carbolyzed antigen of the organism isolated in this case and *Neisseria pharyngis* antiserum was negative in all dilutions.

DISCUSSION

We are at a loss to classify this organism. It has very few of the characteristics of the *Neisseria* group. There have been very few reports in the literature of cases of endocarditis due to gram negative cocci other than the *N. gonorrhoeae*, the *N. intracellularis* and the *Neisseria sicca* group mentioned previously. Two cases were ascribed to *Micrococcus endocarditis rugatus*²³ and one to an unnamed organism.²⁵

SUMMARY

Two cases of bacterial endocarditis with bacteriological, pathological, and serological studies have been reported together with a review of the literature of the rarer causative agents of this disease. One of the organisms belonged to the *Neisseria pharyngis* group while the other was an unidentified gram negative coccus.

BIBLIOGRAPHY

1. LENHARTZ, H.: Die septische Erkrankungen, Nothnagel's specielle Path. u. Therap., 1903, Bd. IV, Theil IV, Abth. I.
2. HORDER, T. J.: Infective endocarditis with an analysis of 150 cases and with special reference to the chronic form of the disease, Quart. Jr. Med., 1908-1909, ii, 289.
3. SIMONS, I.: Critical review; bacterial endocarditis, Quart. Jr. Med., 1913-1914, vii, 291.
4. THAYER, W. S.: Studies on bacterial (infective) endocarditis, Johns Hopkins Hosp. Rep., 1926, xxii, 1-185.

5. BLUMER, G.: Subacute bacterial endocarditis, *Medicine*, 1923, ii, 105.
6. LOCKE, E. A.: Pneumococcus endocarditis, *Boston Med. and Surg. Jr.*, 1924, cxc, 913.
7. THAYER, W. S., and BLUMER, G.: Ulcerative endocarditis due to the gonococcus, *Johns Hopkins Hosp. Rep.*, 1896, vii, 57.
8. WEICHSELBAUM, A., and GHON, A.: Der Mikrokokkus meningitidis cerebrospinalis als Erreger von Endokarditis, *Wien. klin. Wchnschr.*, 1905, xviii, 625.
9. ENDRES, G.: Der Mikrokokkus catarrhalis als Erreger einer Sepsis mit Endocarditis und Nephritis, *München. med. Wchnschr.*, 1925, lxxii, 723.
10. SCHULTZ, O. T.: Acute vegetative endocarditis with multiple secondary foci of involvement due to Micrococcus pharyngitidis siccae, *Jr. Am. Med. Assoc.*, 1918, lxxi, 1939.
11. GRAEF, I., DE LA CHAPELLE, C., and VANCE, M. C.: Micrococcus pharyngis siccus endocarditis, *Am. Jr. Path.*, 1932, viii, 347.
12. GOLDSTEIN, J. D.: Endocarditis due to *Neisseria pharyngis* organism, *Am. Jr. Med. Sci.*, 1934, clxxxvii, 672.
13. KAMMERER, H., and WEGNER, R. N.: Zur Aetiologie der Endocarditis lenta. Micrococcus flavus als Erreger, *München. med. Wchnschr.*, 1914, lxi, 588.
14. HORDER, T. J.: *Trans. Path. Soc.*, London, 1906, lvi, 58.
15. MILLER and BRANCH: Subacute bacterial endocarditis due to a hemolytic hemophilic bacillus, *Arch. Int. Med.*, 1923, xxxii, 911.
16. DICKAR, L.: Acute bacterial endocarditis due to *Bacterium acidi-lactici*, *Arch. Int. Med.*, 1932, xlix, 788.
17. CHALIER and PASSA: De l'endocarditis typhique, *Progres Med.*, 1930, viii, 317.
18. YOUNG and BLUMER: A case of anthrax septicemia in a human being associated with acute anthrax endocarditis and peritonitis, *Bull. Johns Hopkins Hosp.*, 1895, vi, 127.
19. HOWARD, W. T.: Acute ulcerative endocarditis due to the *Bacillus diphtheriae*, *Bull. Johns Hopkins Hosp.*, 1893, iv, 32.
20. DEAN, G.: A case of pyaemic actinomycosis with an actinomycotic endocarditis, *Brit. Med. Jr.*, 1912, ii, 1303.
21. DE LA CHAPELLE, C. E.: Vegetative endocarditis due to the *Brucella melitensis*, *Am. Heart Jr.*, 1928, iv, 732.
22. TEISSIER, GASTINEL, P., and REILLEY, JR.: Plague bacillus acute endocarditis, *Bull. Soc. Med. d. Hop.*, 1921, xlv, 1268.
23. WEICHSELBAUM, A.: Beiträge zur Aetiologie und pathologischen Anatomie der Endocarditis, *Beitr. z. path. Anat. u. z. allg. Path.*, 1888, iv, 125.
24. CALLENDAR, G. R.: Endocarditis of the pulmonic valve caused by Micrococcus endocarditis rugatus, *Am. Jr. Med. Sci.*, 1915, cxlix, 723.
25. COULTER, C. B.: Gram negative micrococcus causing fatal endocarditis, *Proc. New York Path. Soc.*, 1915, xv, 7.
26. ELSEY, W. J., and HUNTOON, F. M.: Studies on meningitis, *Jr. Med. Research*, 1909, xx, 373.
27. WILSON, S. P.: Investigation of certain gram negative cocci met with in nasopharynx with special reference to their classification, *Jr. Path. and Bact.*, 1928, xxxi, 477.
28. WILSON, G. S., and SMITH, M. M.: Observations on gram negative cocci of the nasopharynx with description of *Neisseria pharyngis*, *Jr. Path. and Bact.*, 1928, xxxi, 597.
29. REINHARD, H.: Ein Fall von endokardialen Abklatschtuberkel, *Virchow's Arch. f. path. Anat.*, 1912, ccx, 248.

OBSERVATIONS UPON THE EXPERIMENTAL AND CLINICAL USE OF SULFAPYRIDINE. II. THE TREATMENT OF PNEUMOCOCCAL PNEUMONIA WITH SULFAPYRIDINE*

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THE rational utilization of any promising compound in the field of clinical chemotherapy is dependent upon a knowledge of its absorption by, distribution in, and excretion from the body. Early in the course of our studies upon sulfapyridine, we¹ noted that the drug was not readily soluble, and in comparison with sulfanilamide, poorly absorbed, when it was administered to animals by the oral route. While increasing doses gave blood levels of increasing amounts, these concentrations were not at all proportional to the dose, and certain individual animals showed marked variations from time to time in their ability to absorb the drug. It was also observed that the tissues of the host had the power of conjugating sulfapyridine. Later this conjugated fraction was shown by Marshall and his associates² and by Baines and Wien³ to be acetyl sulfapyridine. The results of certain of our studies upon the concentration of the drug in the blood of animals following single doses of sulfapyridine are shown in table 1.

TABLE I
Blood Levels of Sulfapyridine Following Single Peroral Doses in Mice, Rabbits, Dogs and Man

Species	Dose gm./ kilo p.o.	Blood Levels in mg. %, Hours Following Administration of Sulfapyridine											
		1		2		4		5		8		24	
		F	T	F	T	F	T	F	T	F	T	F	T
Mouse	0.5	15.4		15.6		12.5				6.9		3.2	
"	1.0	23.6	22.9			21.1	21.4			16.0	16.5	0.7	0.6
Rabbit	0.5					2.8	7.9			2.9	7.8	T	4.0
Dog I	1.0	0.8	0.8	2.08	6.3	6.25	6.25			9.1	9.1	1.0	1.0
"	1.0					19.4	19.5			16.7	16.8	1.3	1.4
"	1.0	T	T			9.35	9.44			17.1	17.3	1.2	1.3
Man	0.05	0.55	0.53			3.26	3.2			2.77	2.6	1.8	1.7
"	0.05	T	T			5.0	4.9			4.1	4.4	2.5	2.6
"	0.05	0.5	0.6			4.2	4.0			2.8	3.4	3.1	3.1
"	0.05	1.6	1.7			3.4	3.4			3.1	3.2	3.1	3.1
"	0.10	0.9	1.1					4.6	4.6	4.7	7.4	1.9	2.9
"	0.05	5.9	6.6									0.9	2.4
Infant	I.V.					4.4						0.74	1.23
"	0.1			3.2	3.2	5.6	5.6			5.3	5.4	2.4	2.5
"	0.1			4.1	4.1	3.3	3.6			3.2	3.5	2.0	2.3
												VFT	VFT
												VFT	VFT

F = Free sulfapyridine
T = Total sulfapyridine (including conjugated fraction)

We next investigated the absorption of sulfapyridine when the drug was given to human beings by the oral route. These studies were carried

* Received for publication July 1, 1939.
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This investigation was supported by a grant from The Chemical Foundation, Inc., of New York City.

out by estimating the concentrations of the drug in the blood following single doses and by determining the amount of sulfapyridine excreted in the urine in a given period of time.

It soon became evident that lower concentrations of the drug were to be found in the blood after a given dose of sulfapyridine than would be expected had the same amount of sulfanilamide been administered. It was also observed, as is shown in table 1, that the concentration of the drug in the blood was maintained somewhat better than is the case with sulfanilamide. This latter factor is probably dependent upon a somewhat slower absorption and less rapid excretion of the drug.

During the past year we have noted marked variations between individuals in their ability to absorb sulfapyridine, and we have also observed similar variations in the same individual when the drug was given over a period of time. Thus, in one instance, an adult receiving a total of 9 grams of sulfapyridine during the first 24 hours of an illness had a concentration of 3.3 milligrams per cent of the free drug with a total of 5.0 milligrams per cent, while another patient of the same weight had a concentration of 9.0 milligrams per cent of the free drug and 11.1 milligrams per cent total following the same dose over the same period of time. Another factor which militated against rational therapy with the drug was the tendency on the part of the tissues of certain individuals to conjugate a large proportion of the absorbed drug to the inactive acetyl derivative. Thus, we have repeatedly noted in certain individuals that despite an adequate absorption of the drug (as measured by the total sulfapyridine content of the blood) satisfactory therapeutic levels of the free drug were difficult to obtain and maintain because from 40 to 80 per cent of the absorbed drug had been conjugated to the acetyl form. This excessive conjugation of the drug may be present from the beginning of therapy or it may become progressively more marked as treatment is continued.

The drug is distributed in transudates and exudates as a general rule in about half to three-quarters of the amounts present in the blood. In chart 1 are shown the blood and spinal fluid values for the drug that were obtained in specimens from a patient who was admitted to the hospital with a presumptive diagnosis of pneumococcal meningitis. (Actually the disease was found to be due to anaerobic streptococci.) This chart also clearly indicates the rapidity with which high concentrations of sulfapyridine may be obtained in the blood and spinal fluid following the intravenous use of the sodium salt of sulfapyridine.

During the past year, various observers have noted that pleural exudates obtained from patients receiving sulfapyridine showed excessively high concentrations of the drug (?) when determinations of these values were made according to the method described by Bratton and Marshall.⁴ This gave rise to the supposition that the drug might be concentrated in pleural exudates. During the past winter we made a survey of the possible factors involved in this matter and finally were able to demonstrate that the

local anesthetic, generally procaine hydrochloride (para aminobenzoyl-diethyl aminoethanol hydrochloride), which was used to anesthetize the tissues, was capable of giving a color reaction quite similar to that produced by sulfanilamide or sulfapyridine. This occurs because of the pres-

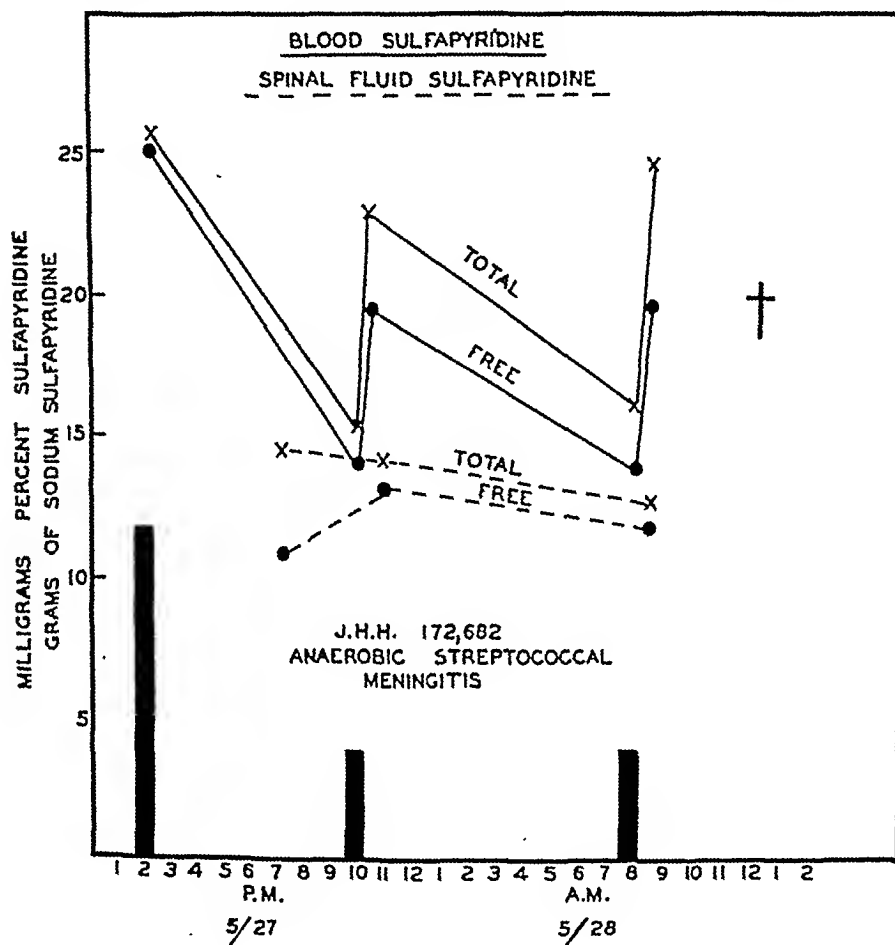


CHART I. The concentrations of sulfapyridine noted in the blood and spinal fluid of a patient receiving sodium sulfapyridine by the intravenous route.

ence of a "free" amino group in this type of local anesthetic. Hence, we feel justified in stating that in our experience the excessive values for sulfapyridine which have been occasionally reported in pleural exudates may result from the contamination of the exudate by a local anesthetic of the procaine type.

As far as we have been able to ascertain, the absorption of sulfapyridine as determined by the amount of drug excreted in the urine, confirms our previous observations on absorption which were based upon its concentration in the blood.

The results of the experiments designed to determine the amount of and rate of excretion of the drug are recorded in table 2. As will be noted, following single doses of the drug, excretion of sulfapyridine is greatest in the first 48 hours, but it may take four days or more to completely rid

TABLE II
Urinary Excretion of Sulfapyridine Following Administration of Single
and Repeated Doses of the Compound

Subject	Dose of Compound	Volume of Urine, Excretion in mg. %, Days														Total Drug Excreted	% Dose Excreted
		1			2			3			4						
		U.V. c.c.	F	T	U.V. c.c.	F	T	U.V. c.c.	F	T	U.E. c.c.	F	T				
J. C.	Single 0.05 gm./kilo p.o. Total =3.0	1875	32.6	48.6	2775	23.5	36.6	1875	11.6	25	1660	6.4	13.2	2.37	79		
S. B.	Single 0.1 gm./kilo p.o. Total =5.7	2850	25	48.8	2600	11.9	45.5	1650	4	22.5		T	T	2.9	51		
E. P.	Single 0.1 gm./kilo p.o. Total =6.8	1675	50	79	900	31.2	141.5	1000	4	16.8		T	T	2.34	39		
J. B.	3.6 gm. per day p.o.	1440	30	155	1520	40.8	137	1350	53.6	166				6.55	60		
H. W.	3.6 gm. per day p.o.	1840	62.5	105	1780	47	89.9	2640	40	77				5.52	51		
D. J.	3.6 gm. per day p.o.	2130	36.4	107	2240	31.3	95.7	2310	38.1	111				6.97	64		
W. B.	2.4 gm. per day p.o.	1410	24.9	131.5	1630	22.2	126	1120	20	114				5.16	86		
W. B.	Single 3.46 gm. I.V.	1625	49.4	134	2915	29.1	108.2	1915	1.7	6.6	3450	1.2	2.3	2.52	72.6		

U.V. = Urine volume. F = Free sulfapyridine. T = Total sulfapyridine (includes conjugated fraction).

the body of the drug. This is to be contrasted with the excretion of sulfanilamide which, under similar conditions, would be complete in about 72 hours. It is also of interest to note that from 39 to 79 per cent of the ingested drug was recovered from the urine in the four day period.

In the four patients who were convalescent from disease and to whom doses of the drug were being given at regular intervals, studies made over a period of three days showed that from 51 to 86 per cent of the ingested drug was being excreted in the urine. These figures are, in general, considerably lower than would be expected if sulfanilamide had been prescribed. and while we have not measured the amount of drug excreted in the stool. we believe the figures dealing with the excretion of sulfapyridine in the urine represent fairly accurate data as to the amount of the drug actually absorbed from the gastrointestinal tract.

Another factor of some consequence which is brought out in table 2 is that, as a rule, the percentage of *conjugated sulfapyridine* is quite high in the urine. This is, of course, of considerable importance when the question arises as to the use of the drug in certain types of urinary tract infections, because the conjugated form is known to be inactive. Then, too, the fact that acetylsulfapyridine is so poorly soluble tends to make it precipitate out in the urine of many patients. The crystals, which initially

are small, and boat or spear head-shaped, may coalesce and form calculi such as have already been reported as occurring in the urinary tract of animals and human beings.⁵⁻⁷

The difficulties which we had encountered in certain patients in either obtaining or maintaining a proper concentration of "free" sulfapyridine in the blood, led Dr. E. K. Marshall, Jr. and one of us⁸ to try the therapeutic effects of the sodium salt of sulfapyridine by the intravenous route. As will be seen in table 1, the intravenous injection of 0.05 gram per kilogram of body weight promptly gave a blood level of slightly over 5 milligrams per cent. This level was moderately well maintained over a period of from six to eight hours. In table 2, data are given concerning the excretion of sulfapyridine over a period of four days following the injection of a single dose of sodium sulfapyridine. The observations which we have made concerning the absorption of sulfapyridine, its distribution through the body and its excretion have been substantiated by the reports of several other observers.^{3, 9, 10}

THE CLINICAL USE OF SULFAPYRIDINE IN THE TREATMENT OF PNEUMOCOCCAL PNEUMONIA

During the past year we have used sulfapyridine in the treatment of a wide variety of infectious diseases. As a result of our experience up to the present time, we feel justified in stating that sulfapyridine is superior to sulfanilamide in the treatment of pneumococcal, staphylococcal and possibly Friedländer's bacillus infections. In these infections the experimental and clinical evidence definitely favors the use of sulfapyridine. In other types of infection, reliable data are not as yet at hand.

There have been numerous reports¹¹⁻²⁵ concerning the use of sulfapyridine in the treatment of pneumococcal pneumonia in children and adults. In their original communication, Evans and Gaisford¹¹ reported that they had treated with sulfapyridine 100 patients who were suffering from lobar pneumonia, and that in this group the case fatality rate was 8 per cent, this to be compared with a fatality rate of 27 per cent in a group of 100 patients who had received symptomatic treatment for lobar pneumonia. While the types of infecting pneumococci were not determined in the majority of these patients, and no data were reported as to the incidence of bacteremia, this communication of Evans and Gaisford is very significant of the therapeutic effects of sulfapyridine in lobar pneumonia. With the exception of this report in which adequate numbers of patients were discussed, many of the early communications, dealing with the use of the drug in pneumonia, were based upon individual cases or upon small groups of patients. However, in the issues of the *Journal of the American Medical Association* and *The Lancet* for February 11, 1939, Flippin and his associates¹⁴ and Agranat et al.¹⁵ described two large series of pneumonia patients who had been treated with sulfapyridine.

In the report of Flippin and his associates¹⁴ the chemotherapeutic effects of the drug were studied in 100 patients ill with lobar pneumonia. In each instance a recognized type of pneumococcus was isolated from the sputum, and in 96 of the patients a blood culture was taken. A review of these cases shows that the distribution of the etiological types of pneumococci was not unusual, in that 83 per cent of the pneumonias were caused by organisms that belonged to the first eight types of pneumococci. However, the fact that the majority of the pneumonias were associated with types of pneumococci which produce the more severe forms of the disease was offset by two factors, the first being that the pneumonias occurred in the late summer, fall and early winter, while the second was that 60 per cent of their patients fell into the 39 year or under, age group. Eight of these hundred patients had positive blood cultures. Four patients succumbed to their infection. (Three patients whose disease terminated in death were excluded from this series because they died in less than 12 hours after treatment was started.) Despite the fact that the patients reported upon were in young age groups, that the bacteremic incidence was low and that the pneumonias were occurring during the fall and early winter, it seems certain to us, after reviewing this paper, that the drug was influencing favorably the course of lobar pneumonia.

It is more difficult to assess the results obtained by Agranat and his co-workers¹⁵ in South Africa, because in many of the patients the type of infecting pneumococcus was not determined, blood cultures were not done, and a certain number of their treated and control patients had previously been inoculated with a pneumococcal vaccine. It was noted that in native miners the case fatality rates on the treated and untreated groups showed no significant difference, while in non-mining pneumonia patients, both colored and European, those who were treated with sulfapyridine showed a marked reduction in the case fatality rate as compared with the control group. In all of the treated groups the course of the pneumonia seemed to be altered in that the average rate of the return of the temperature to normal was accelerated as compared to the control groups, and despite the lack of certain essential data, the conclusion that sulfapyridine was "a valuable drug for the effective treatment of pneumonia both in Europeans and in natives" seems to be justified.

Duncan Graham and his associates²⁰ have reported a carefully studied series of patients ill with pneumococcal pneumonia and treated with sulfapyridine. Every effort was made by these observers to establish the etiological agent in the pneumonias. A perusal of their data shows an essentially normal distribution of the types of pneumococci, an age group distribution which favors the severity of the disease, a bacteremic rate which was high (34 per cent) and (at least in the early part of their studies) an untreated control group of 30 patients in which the case fatality rate was 23.3 per cent. As a result of therapy with sulfapyridine the case fatality rate in the treated group of 50 patients was reduced to 6 per cent

and in the 17 patients who had a bacteremia only three, or 17.6 per cent, died. These results were certainly striking.

In their original communication Evans and Gaisford¹¹ referred briefly to the apparently successful use of sulfapyridine in the treatment of pneumonia in children. Barnett and his associates¹⁶ have reported that the drug gave good results in the therapy of pneumococcal pneumonias in infants and children. They advocate its prompt use in pneumonia, particularly if the pneumonia is suspected of being caused by the pneumococcus.

Hodes and his associates¹⁰ have described their experience with the drug in 71 infants and children who were ill with pneumococcal pneumonia. In 33 of the patients the disease was primary, while in 38 the pneumonia was associated with measles. In all instances pneumococci, identified by type-specific sera, were obtained from the rhinopharynx, and consolidation of the lungs was shown by roentgenograms. In the group of primary pneumonias type 14 seemed to be the most common organism, and in the pneumonias associated with measles, type 14 was also commonly found as the etiological agent. Composite average temperature charts of these two groups of patients showed that the temperature reached normal in 40 hours after the beginning of treatment in the group of primary pneumonias, and in 30 hours in the group of pneumonias which was associated with measles. None of the 71 patients died. It was our privilege to see a number of the patients included in this series, and it was often striking to note the immediate marked clinical improvement which followed the institution of sulfapyridine therapy.

Our own experience with the use of sulfapyridine dates from July 1938, when, following preliminary laboratory observations upon the efficacy of the drug in the control of experimental pneumococcal infections in mice, its toxicity in animals and its rate of absorption and excretion in animals and human beings, we decided that our findings warranted careful clinical trials of the drug in pneumococcal pneumonia.

For more than 15 years, it has been the practice in The Johns Hopkins Hospital to employ specific pneumococcal antisera in the treatment of pneumococcal pneumonia. The results obtained over a period of years from the use of specific antisera in types I and II pneumococcal lobar pneumonia were very satisfactory, and during the past three years, following the introduction of specific horse and rabbit antisera, not only for types I and II, but also for type III and the higher types IV to VIII and XIV, we have been able to increase the number of patients who received the benefits of serum therapy in the course of lobar pneumonia.

During the past three years when sera of high potency for types I to VIII and XIV have been available, and especially since we have controlled the administration of antipneumococcal serum with the specific capsular polysaccharide skin test, our results in the therapy of pneumococcal pneumonia have been excellent. Therefore, at the beginning of our clinical studies with sulfapyridine, we did not feel that enough evidence was at hand to

justify the abandonment of serum in favor of the drug. We accordingly decided to use specific antiserum in those cases for which it was available and to give sulfapyridine to patients ill with pneumococcal pneumonia, for the treatment of which serum was not available and to those in whom the use of serum was contraindicated because of a history of asthma or hypersensitivity to serum. This plan was adhered to until early in February 1939, at which time, due partly to the excellent results already obtained from the peroral use of sulfapyridine in patients ill with lobar pneumonia, and partly to the fact that the use of sodium sulfapyridine by the intravenous route had been demonstrated to be entirely feasible, we decided to discontinue the primary use of specific pneumococcal antisera and to depend upon sulfapyridine and sodium sulfapyridine for the treatment of patients ill with lobar pneumonia.

It has for many years, been the custom at The Johns Hopkins Hospital to make every effort to type pneumococci isolated from the sputum, blood or exudates of patients ill with lobar pneumonia. The mouse-inoculation test, Avery tube method and the usual cultural methods of isolating pneumococci were used. When pneumococci were isolated, typing by macroscopic agglutination tests was always attempted. More recently the "Quellung" reaction of Neufeld has been added to these procedures. Thus, the patients described in this study have not only had the usual physical and roentgenographic examinations, but also very careful bacteriological studies in an attempt to identify the etiological agent of their pneumonias. If pneumococci were found in the cultures or in the exudate from the mouse peritoneum, attempts were always made to type the organisms either as a check on the Neufeld reaction in the sputum or as a primary diagnostic measure. In those patients in whom it was difficult to obtain sputum, an effort was made to isolate and identify pneumococci in cultures from the rhinopharynx. Cultures of the patient's blood have been made at frequent intervals and if positive, the type of pneumococci was determined. The same has been done with all exudates which have been obtained from patients ill with lobar pneumonia. In certain patients, from whom sputum was not obtained, the identification of the etiological agent of their infection was accomplished by means of lung punctures, and in one instance the type of the pneumococcus was determined by identifying the soluble specific pneumococcal capsular polysaccharide in the urine of the patient by means of precipitin tests. We have not been able to confirm the observation of Telling and Oliver¹² that sulfapyridine therapy alters the capsule of the pneumococcus, thus making the typing of pneumococci difficult after treatment with the drug has been started. It may seem that we have stressed unduly our efforts at typing pneumococci, but we feel that we have been justified in doing so, and that *every effort should be made in the future, when facilities are available, to determine the type of pneumococcus that is responsible for a given case of lobar pneumonia.* It is only by following

such a practice that a real knowledge of the effectiveness of sulfapyridine may be obtained.

From July 1, 1938 until June 20, 1939, 139 adult patients (i.e., over 15 years of age) were treated in The Johns Hopkins Hospital for presumptive pneumococcal pneumonia. As is shown in table 3, pneumococci, identified by specific antisera, were obtained from the sputa of 124 of these patients, in five individuals pneumococci were identified in the sputum but it was not possible to type the organisms, and from 10 patients pneumococci were not isolated at any time during the course of their disease.

TABLE III

The Course of Pneumococcal Pneumonia in Adult Patients in the Johns Hopkins Hospital from July 1, 1938 to June 20, 1939

Type	No. of Cases	Bacteremic Incidence on Admission	No. Cases Treated with			Incidence of Complications	Incidence of Concurrent Disease	Case Fatality Rate
			serum	sulfa-pyridine	serum and sulfa-pyridine			
1	24	6	13	11		2	5	1
2	6	4	1	3	2	4		1
3	20*	1	4	13	3	1	10	2
4	10	1	4	6			5	1
5	5	1	1	3	1	1	3	1
6	1			1			1	
7	11	3	5	6		4		
8	14	3	3	10	1	1	8	1
11	2			2				
12	1			1				
13	1	1		1		1		1
14	3			3		1		
15	1	1		1				
16	2	1		1	1	1		
17	1			1			1	
18	4			4			1	
19	6	1		6		1	2	1
20	4			4		1	2	
22	2			2			2	
23	1			1			1	
24	1			1			1	
25	2			2			1	
32	2			2			2	
Untyped	15			15			6	1
Total 1938-39	139	23 or 16.5%	31 or 22.3%	100 or 72%	8 or 5.7%	18 or 13.7%	51 or 36.6%	10 or 7.2%

* In this group, two patients had more than one type of pneumococcus isolated from their sputum.

On admission to the hospital 23 of the patients were found to be suffering from a pneumococcal bacteremia. Thirty-one of the patients were treated with type specific pneumococcal antisera, 100 patients with sulfapyridine, and eight were treated with type specific serum and sulfapyridine. Eighteen of these patients suffered from a complication resulting from the infection, while 51 had major concurrent diseases which are recognized as

unfavorably influencing the course of pneumonia. Ten of the 139 patients died, thus giving a *case fatality rate of 7.2 per cent*. This case fatality rate is probably the lowest for pneumococcal pneumonia in the history of The Johns Hopkins Hospital.

It is obvious in assessing the results of any type of therapy, that adequate controls should, when possible, be presented. This we are unable to do, but we believe that a review of the course of pneumococcal pneumonia during the past four years in this hospital, will attest the validity of our figures. This is especially necessary in view of the often repeated statement that pneumonia has not been as severe as usual during the past year.

Our data present four possible criteria by which we may judge the validity of our experience during the past year. It is important to know whether the type distribution of pneumococci (as determined by the incidence of types I, II and III pneumonias) was similar to that of previous years, whether the incidence of bacteremia was comparable, whether any shift in the age distribution of the patients had taken place, and whether the occurrence of major concurrent disease was the same as in past years. In the latter category we place heart disease of various types, diabetes, asthma, tuberculosis, chronic alcoholism, pregnancy, and surgical procedures, all of which are known to influence unfavorably the course of lobar pneumonia.

TABLE IV

The Course of Pneumococcal Pneumonia in Adult Patients in the Johns Hopkins Hospital from July 1, 1935 to June 20, 1939

Year	No. Cases	Bacteremic Incidence		No. Cases Treated			Incidence of Complications	Incidence of Concurrent Disease	Case Fatality Rate
		Admission	Late	Specific Serum	Sulfa-pyridine	Serum and Sulfa-pyridine			
1935-1936	157	21 or 13.3% 23 or 14.5%	2 or 1.2% 14.5%	31 or 19.7%			33 or 21%	31 or 19.7%	30 or 19.1%
1936-1937	181	28 or 15.5% 35 or 19.3%	7 or 3.8% 19.3%	46 or 25.4%			27 or 14.8%	64 or 35.3%	38 or 21%
1937-1938	148	20 or 13.5% 24 or 16.5%	4 or 3% 16.5%	61 or 40.1%			20 or 13.5%	62 or 40.2%	26 or 17.6%
1938-1939	139	23 or 16.5%		31 or 22.3%	100 or 72%	8 or 5.7%	18 or 13.7%	51 or 36.6%	10 or 7.2%

In table 4 is outlined the course of pneumococcal pneumonia in adult patients in this hospital from July 1, 1935 until June 20, 1939. While the data are not included in table 4, we may state that the incidence of types I, II and III pneumococcal pneumonias was 35.6 per cent, 32.5 per cent, 33.7 per cent and 35.9 per cent per year from 1935 to 1939. Hence, our

record of this year is not dependent upon a shift in the type distribution of pneumococci.

The incidence of bacteremia as shown in table 4 is of considerable interest and importance. It is noteworthy that during the past year 16.5 per cent of the patients who were ill with pneumonia had a positive blood culture at the time of their *admission* to the hospital, and that *none* of the patients whose blood cultures were negative upon entrance to the hospital subsequently developed a positive blood culture. This is in contradistinction to each of the previous years during which a certain number of patients ill with pneumonia entered the hospital without bacteremia and subsequently developed it. Hence, while the total bacteremia rate is slightly lower this year than in the previous two years, the rate on *admission* is the highest of the last four years.

We have determined the prognostic importance of the presence of bacteremia upon the course of pneumonia during the past four years. In table 5 are data which bear upon this point. It is to be noted that 30 out

TABLE V

The Case Fatality Rates in Untreated and Treated Adult Patients Ill with Bacteremic Pneumococcal Pneumonia in the Johns Hopkins Hospital from July 1, 1935 to June 20, 1939

Type	Untreated	Deaths	Serum Treated	Deaths	Sulfa-pyridine Treated	Deaths	Serum and Sulfa-pyridine Treated	Deaths
1	1	1	28	10	3			
2	1	1	3	2	1		2	1
3	8	8	3	2				
4					1	1		
5	3	2	1	1			1	1
7	1		7	2				
8	4	3	4	1	3			
10	4	3						
12			1					
13					1	1		
14			2	1				
15					1			
16					1			
19					1	1		
20	1							
25	1	1						
Group IV	14	11	.					
Total	38	30 or 80%	49	19 or 38%	12	3 or 25%	3	2 or 66%

of 38 untreated patients ill with pneumonia and in whom the presence of bacteremia had been determined, succumbed to their disease. A review of the eight patients who survived shows that with one exception the colony count of pneumococci was below one per cubic centimeter of blood, the exception showing three colonies per cubic centimeter. Also, with one exception, only a single blood culture was positive for pneumococci. These

figures are in accord with the general opinion that the presence of bacteremia is of extremely bad prognostic significance in the course of pneumococcal pneumonia in adult patients.

The age of the patient has a definite bearing upon the course and severity of pneumococcal pneumonia. The prognosis in this disease becomes less favorable as the age of the adult patient increases. Hence, it is of importance in evaluating our results during the past year to make certain that there has not been a significant shift in the age distribution of the treated patients. In table 6 is shown the percentage of patients in various age groups. It is clear that there has not been any significant change in the age-distribution of our pneumonia patients during the past year.

TABLE VI
Age Incidence of Adult Patients Ill with Pneumococcal Pneumonia in the
Johns Hopkins Hospital from July 1, 1935 to June 20, 1939

Year	15-19 years	20-29 years	30-39 years	40-49 years	50-59 years	60-69 years	70-79 years	80-89 years
1935-36	9.3%	29.7%	28.2%	15.4%	10.3%	3.8%	2.6%	0.7%
1936-37	8.4%	24.3%	26.0%	16.4%	11.9%	7.9%	4.0%	1.1%
1937-38	14.2%	22.9%	17.2%	22.0%	11.9%	8.6%	2.4%	0.8%
1938-39	5.1%	22.0%	28.8%	20.3%	8.5%	11.0%	4.3%	0.0%

If a patient ill with pneumonia is suffering from one or more other major diseases, his chances of recovering are impaired. The same holds true for pregnant women and for patients who have undergone a recent major surgical operation. As is shown in table 4, the incidence of concurrent disease during the past year did not vary markedly from that reported during the previous three years.

We feel justified, therefore, on the basis of the data which we have just presented, in concluding that the pneumonias which we have seen in adult patients in The Johns Hopkins Hospital during the past year were as severe as those observed during the period from 1935 to 1938. It is logical, therefore, to attribute the marked decline in the case fatality rate in pneumococcal pneumonia noted during the past year to improvements in our treatment of pneumonia, rather than to the vagaries of chance, or to a sudden decline in the "virulence" of the pneumococcus.

During the past year we treated 31 patients suffering from lobar pneumonia with type specific pneumococcal antisera. These and certain other patients so treated will be included in a separate report by Dr. W. Barry Wood, Jr. In this same period of time 100 patients have been treated with sulfapyridine and eight have been treated with sulfapyridine in combination with type specific antiserum.

The course of pneumonia in those patients who were treated with sulfapyridine is outlined in table 7. It is to be noted that 56 per cent of this group of patients would ordinarily have been treated with type specific sera

TABLE VII

The Course of Pneumonia in Patients Treated with Sulfapyridine

Type	No. of Cases	Bacteremia		Incidence of Complications	Incidence of Concurrent Disease	Toxic Reactions	Case Fatalities
		Co./c.c.	No.				
1	11	36/c.c.	3	Pleural Effusion 1	4	1	
2	3	++	1	Pleural Effusion 2	1		
3	13	4/c.c.			7	1	
4	6	+	1		3	1	1
5	3				3		
6	1				1	1	
7	6				1	1	
8	10	+++	3	Empyema 1	5		
11	2						
12	1						
13	1	+	1	Empyema 1			1
14	3				1		
15	1	+	1			1	
16	1	21/c.c.	1		2		
17	1				1		
18	4				1		
19	6	6/c.c.	1	Pleural Effusion 1	3		1
20	4				1		
22	2				2		
23	1				1		
24	1						
25	2						
32	2						
Untyped	5				2		
No. Pneu.	10				5	1	1
Total	100		12	5	42	7	4

of types I to VIII, or XIV. Twelve per cent of these hundred patients had positive blood cultures, and five developed a complication associated with their pneumonia. Forty-two per cent of the patients had major concurrent diseases, while seven suffered from severe toxic reactions due to drug therapy other than those of nausea and vomiting. Three of the patients died, one 45 minutes after the first dose of sulfapyridine, a second six hours after the initial administration of the drug and the third (who probably had bilateral empyema when treatment was started) on the third day of therapy.

The clinical response of these patients to sulfapyridine therapy was, as a rule, quite prompt, and this was especially true when blood concentrations of free sulfapyridine of 4 milligrams per cent or more were reached within the first 24 hours of treatment. The clinical course of pneumonia associated with bacteremia and the response of the disease to sulfapyridine therapy is shown in the temperature records of four patients which are portrayed in chart 2. As will be noted, in each case shown in this chart, the concentration of free sulfapyridine in the blood was 4 milligrams per cent or more within the first 24 hours of treatment.

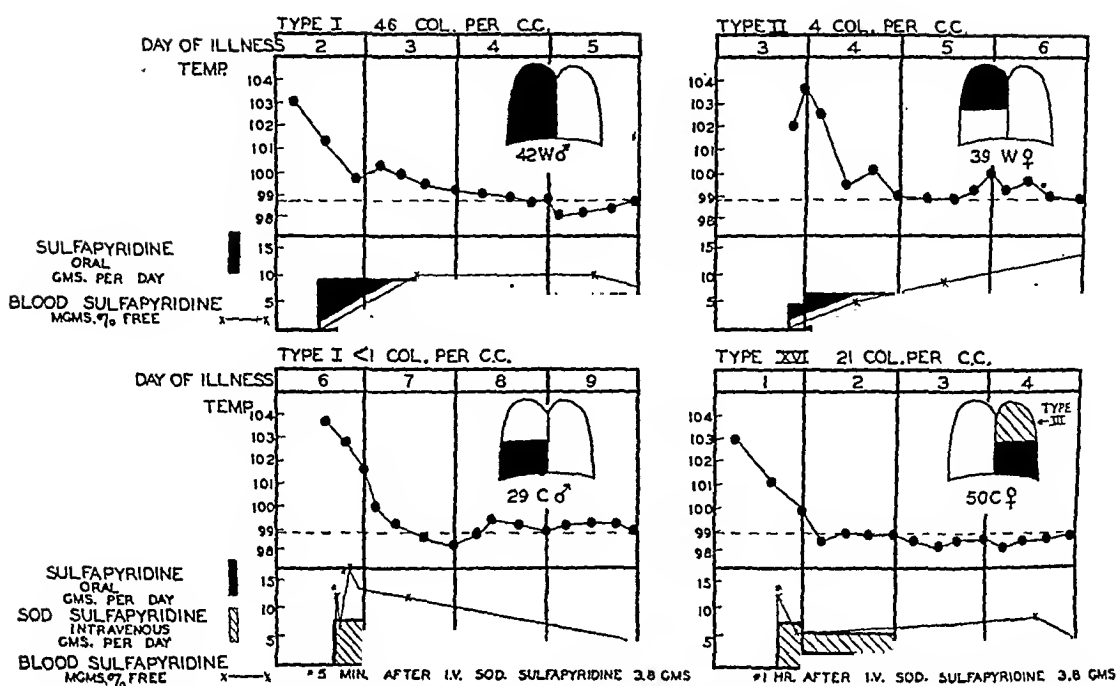


CHART II. Representative cases of pneumococcal pneumonia with bacteremia treated with sulfapyridine and sodium sulfapyridine.

It has been our practice to continue therapy with sulfapyridine until the patient is completely convalescent, and the signs of the disease have disappeared. The response to the drug is frequently very dramatic, and one may be tempted to discontinue sulfapyridine, especially if nausea and vomiting are present as a distressing side effect of the drug. Such a procedure generally results in a recurrence of the disease. Chart 3 shows two such instances.

The first patient was an elderly woman who because of nausea and vomiting refused sulfapyridine after 36 hours of treatment. Although the temperature was normal at the time the drug was discontinued, a secondary rise occurred 40 hours after sulfapyridine had been stopped. Treatment with the drug was resumed, the temperature quickly returned to normal, nausea and vomiting recurred, and the patient again refused to take any more sulfapyridine. As will be noted, a rise in temperature accompanied by a spread in the pneumonic process occurred within 24 hours. Further treatment with sulfapyridine was not attempted and the patient eventually recovered.

The second patient represents an individual in whom the dose of sulfapyridine was decreased too rapidly. On the fifth day of his disease, when the temperature spiked upwards, it was thought that the fever was a toxic manifestation of the drug and sulfapyridine was discontinued for 24 hours. At this point the patient's blood culture was negative. The concentration of the drug in the blood fell practically to zero in the 24 hours after the drug was stopped. On the sixth day it became clear that the febrile reaction

was due to the development of an empyema. Despite intensive oral sulfapyridine therapy, the blood cultures became positive again, the course of the empyema was unchanged, and a closed drainage eventually had to be performed.

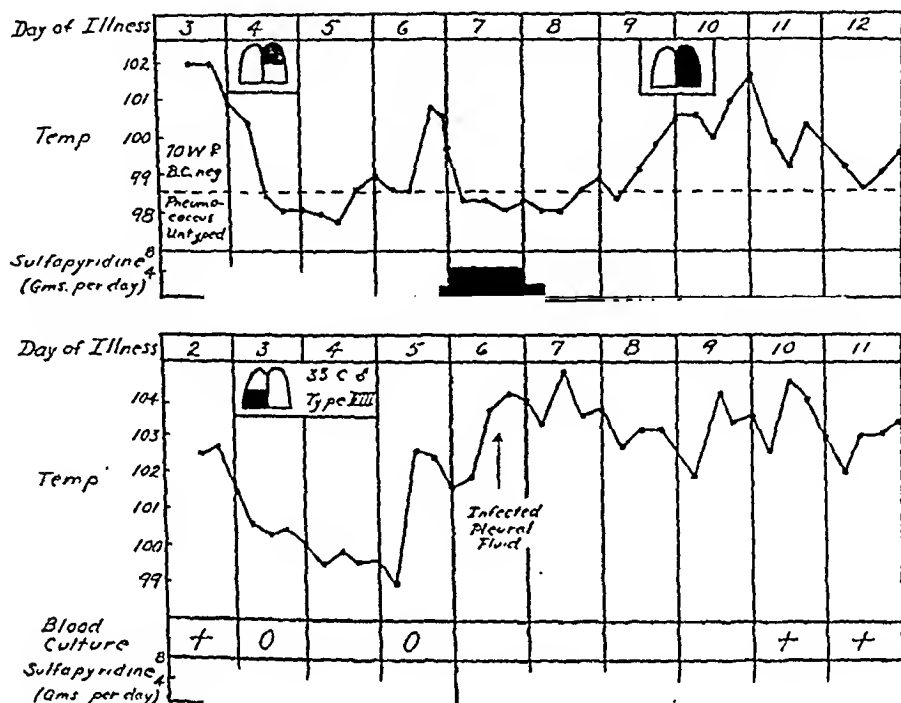


CHART III. Relapse of pneumococcic pneumonia due to inadequate treatment with sulfapyridine.

The evolution of the clinical course of pneumonia in patients who are treated with sulfapyridine varies considerably. In patients who receive adequate therapy and in whom effective concentrations of the drug in the blood are rapidly obtained, the temperature generally returns to normal within 18 to 48 hours after the beginning of treatment. The elevated pulse rate, as a rule, is slower in returning to its normal value. The respiratory rate generally decreases as the temperature recedes, but in certain instances, (especially if the pneumonia is extensive) the respirations may be rapid for 24 to 48 hours after the temperature has been normal.

There are marked and unpredictable variations in the evolution of the physical signs of pneumonia in patients who are treated with sulfapyridine. The existing signs of consolidation may disappear with great rapidity as the temperature comes to normal or as we have frequently noted, these signs may become much more marked over a period of several days after the fever has disappeared. It has seemed to us in many instances that the drug, while bringing about a marked betterment in the general well-being of the patient, has not altered the usual evolution of the pneumonic process in the lungs. We have not observed that therapy with sulfapyridine prolongs the course of resolution of pneumonic processes. It is important,

therefore, as we have already shown in chart 2, to continue the drug until signs of resolution are complete, if relapses of the disease are to be avoided.

Eight patients have been treated with sulfapyridine in combination with type specific pneumococcal antiserum during the past year. Two of these patients were ill with type III pneumonias, and because their response to drug therapy was slow, they were given specific antiserum which brought about a prompt recovery. One patient entered the hospital ill with a type VIII pneumonia and meningitis and died after eight hours of combined therapy. A fourth patient who had been treated with type V antiserum, had an acute bacterial endocarditis which was fatal in spite of sulfapyridine therapy. A fifth patient received sulfapyridine after an intravenous injection of serum had precipitated a moderate anaphylactic attack. A sixth patient ill with a mixed type III and X pneumonia was treated with type III specific antiserum and sulfapyridine. Two patients received adequate treatment with sulfapyridine both by the oral and intravenous routes without bringing their disease under control, and because of their lack of response to the drug were finally treated with specific pneumococcal antisera. These patients are of special interest because they represent definite failures of sulfapyridine therapy.

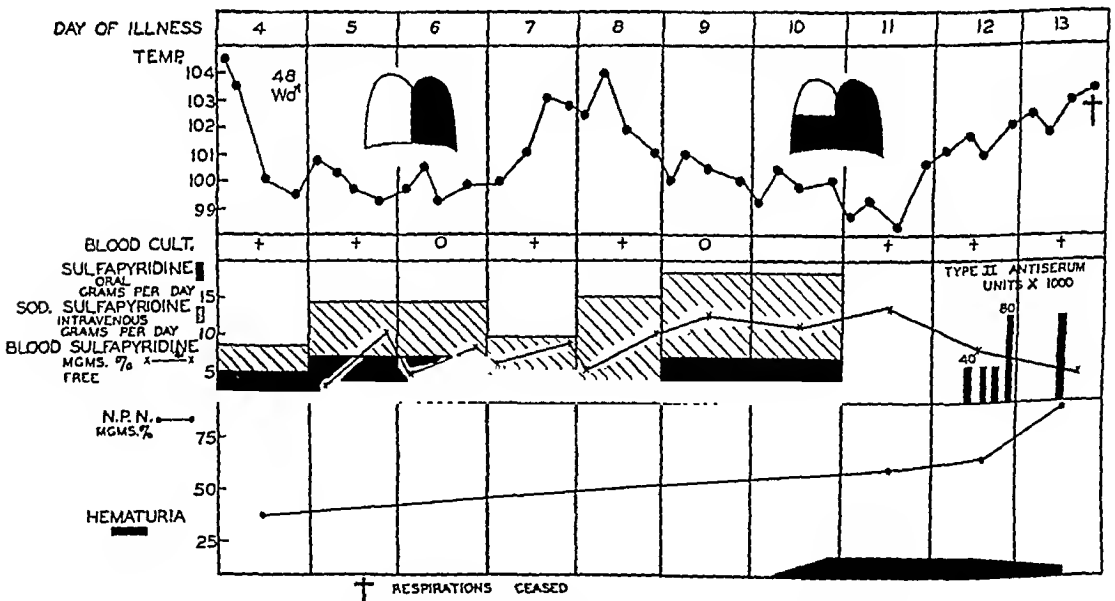


CHART IV. Case of type II pneumonia which failed to respond to intensive treatment with sulfapyridine.

The course of the first of these patients is outlined in chart 4. This man entered the hospital on the fourth day of a type II pneumonia, with involvement of the entire left lung. He seemed quite ill and intensive therapy with sulfapyridine by the oral and intravenous routes was begun. The initial blood culture showed type II pneumococci. It seemed as though the patient was making a good response to treatment during the first 48

hours, but then, despite intensive therapy and the maintenance of an adequate concentration of the drug in the blood, the disease progressed. On the tenth day hematuria developed and the drug was stopped. Within 24 hours the temperature began to rise, the hematuria increased, the urine volume decreased, the non-protein-nitrogen was found to be elevated, and the patient became critically ill. Specific serum therapy was instituted, but it was unsuccessful and the patient died. At autopsy acetylsulfapyridine calculi were found in both kidney pelves.

This experience made us realize that we could not rely upon sulfapyridine therapy in every instance, and that we would encounter certain patients in whom intensive therapy with the drug would be to no avail. The course of another such patient is shown in chart 5. This patient, a 40

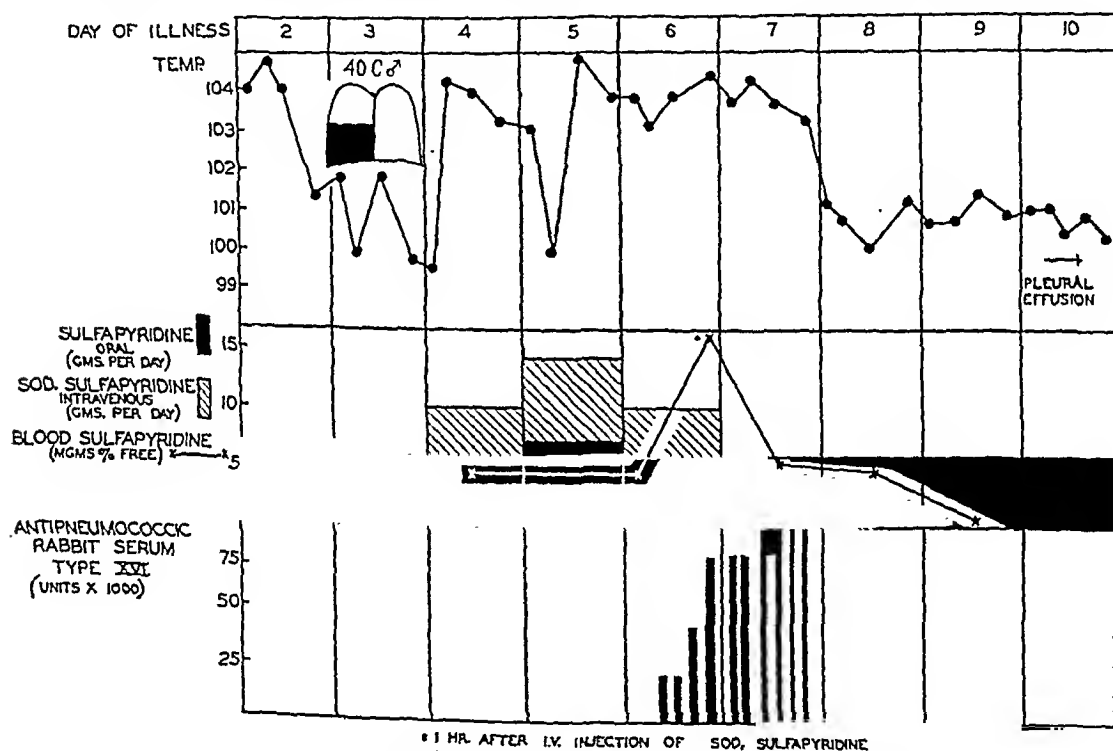


CHART V. Case of type XVI pneumonia which failed to respond to treatment with sulfapyridine.

year old colored man, entered the ward on the second day of a type XVI pneumonia with one lobe involved by the pneumonic process. The blood culture was negative and remained so throughout the course of his disease. Oral therapy with sulfapyridine was started and during the first 48 hours it seemed as though he was making a fair response to the drug. On the fourth day the temperature became sharply elevated, and treatment by the intravenous route was begun. Despite intensive therapy, the disease process was not brought under control, and on the sixth day serum therapy was started. A total of 760,000 units of type XVI antipneumococcal rabbit serum was required to induce a partial crisis in this patient. Even so, the

temperature did not come down to normal and the patient eventually developed a sterile pleural effusion.

The histories of these two patients are of the greatest importance because they indicate that therapy with sulfapyridine will not give satisfactory results in all patients ill with pneumococcal pneumonia, and that the physician must be prepared to administer type specific antipneumococcal serum in such instances. We are uncertain as to how long one should rely upon sulfapyridine therapy in a given patient who does not seem to be responding promptly to treatment. Our impression at present is that if intensive sulfapyridine therapy with the immediate attainment and maintenance of concentrations of 4 milligrams per cent or more of the drug in the patient's blood does not result in a marked improvement in his condition within 48 hours, therapy with type specific antipneumococcal serum is indicated.

The problem of whether treatment with type specific antisera combined with adequate doses of sulfapyridine might not be the best method of therapy for pneumococcal pneumonia, has not been settled. We can see no objection, except that of the cost of serum, to such a procedure and there are theoretical considerations which indicate that combined therapy might be the ideal method of treatment. Certainly, if faced with a severe pneumococcal pneumonia due to a type of pneumococcus for which a potent serum was available, we would not hesitate to use serum and sulfapyridine.

It has been said that the "day of serum therapy" in pneumonia is limited because of the introduction of sulfapyridine as a therapeutic agent in this disease. This we believe to be a careless over-statement. We have already shown that certain cases of pneumonia may prove to be resistant to treatment with the drug, and there are certain considerations which lead us to believe that in severe cases of pneumonia, combined serum and sulfapyridine therapy may be the best method of treatment. Then, too, as time goes on, it will be found that an increasing number of people will be intolerant to sulfapyridine, and if such individuals develop pneumonia, treatment with serum will be the only specific method of therapy that will be possible.

In the summer and fall of 1938 it was our practice to administer 1.0 gram (15 grains) of the drug every four or six hours. However, as our studies progressed, it became evident that if the infection was to be brought under control rapidly, an initial dose of 4.0 grams of the drug followed by 1.0 gram every four hours offered the best chance of rapidly combatting the infection. At the present time our system of dosage for adult patients who are moderately ill with lobar pneumonia is as follows:

1. 4.0 grams *stat.* as soon as the clinical diagnosis of pneumonia is established.
2. Then, 1.0 gram every four hours (day and night) until the temperature has been normal for 48 hours.
3. Then, 1.0 gram every six hours until resolution is well under way.

4. Finally, 0.5 gram four times a day until the patient is ready to leave his bed.

If, however, on the day after treatment with sulfapyridine has been started, the rectal temperature of the patient is not below 101° F. and the concentration of "free" sulfapyridine in his blood is under 4 milligrams per cent, it is our practice to give the patient one dose of 0.06 gram per kilogram of body weight of monohydrate sodium sulfapyridine by the intravenous route. The peroral administration of the drug is continued as before.

In preparing sodium sulfapyridine for intravenous use the required amount of the drug is weighed out and dissolved in enough *sterile, distilled* water to make a 5 per cent solution. Sodium sulfapyridine is unstable to heat and, hence, such solutions cannot be sterilized. However, since a 5 per cent solution of sodium sulfapyridine has a pH of 10.7 to 10.8, it is, in itself, somewhat bactericidal. The drug is *always administered by the intravenous route*, and great care must be taken to be sure that the needle is well in the vein before the injection is started in order to avoid getting any of the solution into the tissues. As with alkalinized arsphenamine, the injection of the sodium salt into the tissue results in a painful area of induration which may eventually slough. With the needle in the vein, the solution is injected slowly, 1 minute being required for the injection of 5 cubic centimeters, thus making the time of injection from 10 to 15 minutes in the average adult.

In pneumonia patients who are seriously ill we prefer to start treatment by the intravenous injection of solutions of sodium sulfapyridine in order that adequate concentrations of the drug may be quickly obtained. Hence, we generally give an initial dose of the monohydrate sodium salt based upon 0.06 gram per kilogram of body weight and repeat this dose in from four to six hours. Such a dose will produce a blood concentration of about 5 milligrams per cent of the drug within a few minutes after it is injected. At the same time we begin peroral medication using 1.0 gram of sulfapyridine every four hours. This type of combined peroral and intravenous therapy permits one to obtain and maintain adequate concentrations of the drug in the blood of patients who are seriously ill. In our experience we have rarely had to use more than two intravenous injections of the drug and have found that after the first few hours it is safe to rely upon peroral medication alone. It is to be remembered that within a very short time after a solution of the sodium salt is injected, the sodium ion is probably split off and the substance circulating in the blood is sulfapyridine.

It is often difficult to obtain and maintain effective blood concentrations of sulfapyridine in patients because of the nausea and vomiting caused by the drug. In these individuals the intravenous use of sodium sulfapyridine is advantageous. Sodium sulfapyridine is also a valuable adjunct in the treatment of pneumococcal infections in patients whose tissues conjugate the drug to a high degree. In such instances the judicious use of

sodium sulfapyridine makes it possible to maintain adequate concentrations of the drug. It must be remembered, however, that the tissues will conjugate sulfapyridine which is given by the intravenous route in the same manner as that given *per os*. Sodium sulfapyridine is also of value in the treatment of patients in whom, because of recent surgical procedures, the peroral use of the drug is undesirable. In all instances, however, it must be kept in mind that following the intravenous use of sodium sulfapyridine, the patient is just as likely to suffer from nausea and vomiting as he is when the drug is given by mouth. There is little reason to believe that the intravenous use of the drug lessens the incidence of nausea and vomiting.

The auxiliary treatment of patients who are ill with pneumococcal pneumonia and who are being treated with sulfapyridine should be essentially the same as that used before the drug was available. *Fluids should not be limited nor should they be forced to extremes.* Our observations lead us to believe that a fluid intake of 3500 cubic centimeters a day is adequate during the first days of treatment, and we force and limit fluids to this level. The diet may be as desired. As far as our experience goes, we have not found that sulfapyridine was incompatible with other drugs and we never hesitate to use them if they are indicated by the needs of the patient. We have not used saline laxatives or cathartics.

In the beginning of our use of sulfapyridine we noted that therapy with the drug was not accompanied by a drop in the CO_2 combining power of the blood and, hence, we thought it unnecessary to use bicarbonate of soda. Recently, however, we have been administering bicarbonate of soda gram for gram with sulfapyridine with the idea of rendering the urine so alkaline (pH 7.5) that the precipitation of acetylsulfapyridine would be hindered. While theoretical conditions indicate that this might be a valuable procedure, enough factual evidence is not at hand to assess the real value of this type of therapy.

THE EFFECT OF SULFAPYRIDINE THERAPY UPON THE COMPLICATIONS OF PNEUMOCOCCAL PNEUMONIA

While the incidence of serious complications has been low in the series of cases which we have just discussed, we are of the opinion that the number of patients observed by us is too small to form a basis for any judgment as to the possible effects of sulfapyridine therapy upon the incidence of complications in the course of pneumococcal pneumonia.

We have tested the therapeutic effects of the drug in three infected empyemas during the past year and in each instance a closed drainage of the empyema eventually had to be done. In one patient suffering from an acute pneumococcal endocarditis, therapy with sulfapyridine was unsuccessful and the patient died. This group of patients is obviously too small to be of much value in assessing this phase of sulfapyridine therapy.

THE TOXIC MANIFESTATIONS OF SULFAPYRIDINE THERAPY

Sulfapyridine produces many of the toxic manifestations which have previously been described in the course of sulfanilamide therapy. It is our impression, based upon the observation of the patients included in this report and upon about 400 other individuals who were ill with miscellaneous infections and treated with sulfapyridine during the past year, that the toxic manifestations of this drug are, with two exceptions, somewhat less common than those of sulfanilamide. Sulfapyridine causes definitely more nausea and vomiting than does sulfanilamide and is known (in its conjugated form) to be responsible for the formation of renal calculi. It is important to remember that if a patient has once had a toxic reaction in the course of sulfanilamide or sulfapyridine therapy, a second and more severe one may occur, if one or the other of these drugs is administered a second time.

Central Nervous System Effects. The most common toxic manifestation of sulfapyridine therapy is nausea and vomiting. This is more common in adults than in children, and occurs more frequently in white patients than it does in negroes. It is frequently quite severe and often renders peroral therapy with the drug difficult. In the series of cases which we have just reported there was but one patient in whom vomiting was so severe that it was thought best to discontinue the drug. It was believed during the early use of sulfapyridine therapy that the nausea and vomiting were the results of gastric irritation produced by the drug. The observations of Marshall and Long⁸ have definitely disproved this hypothesis and show that the vomiting is the result of an action of the drug upon the central nervous system. For this reason the use of demulcents is not indicated in the course of sulfapyridine therapy.

The drug may cause a mild depression in certain individuals, and on two occasions we have encountered patients who suffered from toxic excitement in the course of sulfapyridine therapy. Early in the course of our use of the drug, Dr. James Bordley III pointed out to us that, in addition to a mild depression, certain patients spoke in a slow monotone, had waxy, deliberate movements, thus resembling individuals suffering from a mild attack of encephalitis. This syndrome may persist for several days after the drug has been stopped. We have noted no instance of a toxic peripheral neuritis in the course of therapy with sulfapyridine.

Dermatitis. We have seen several instances of measly eruptions very similar to those occurring in the course of sulfanilamide therapy, in patients who were receiving sulfapyridine. Individuals who are receiving sulfapyridine should keep away from sunlight. In patients developing a rash we have always discontinued the drug.

Fever. Drug fever, similar to that described in the course of sulfanilamide therapy, has been noted in several of our patients who were receiving sulfapyridine. In one instance a patient who had developed drug fever

in the course of sulfapyridine therapy, was noted to have the same toxic manifestation three weeks later when a course of sulfanilamide was instituted. This suggests that a patient who has had a severe toxic reaction to one of this group of drugs may develop the same toxic manifestation when another drug of the same group is prescribed.

Cyanosis. While cyanosis has been observed in our patients, it has occurred less frequently and with a lesser degree of intensity than has been our experience in the course of sulfanilamide therapy. We have not seen any deleterious effects resulting from the administration of the drug to patients who were ill with pneumonia and already suffering from cyanosis. Barnett and his associates¹⁰ have reported that the cyanosis is due to formation of methemoglobin.

Acidosis. As far as we know, sulfapyridine does not produce acidosis.

Renal Irritation. Antopol and Robinson⁵ have reported that they found acetylsulfapyridine uroliths in the urinary tracts of rats, rabbits and monkeys who had been fed large amounts of sulfapyridine. Gross and his associates⁶ independently observed the formation of similar concretions in rats. Lawrence²⁶ suggested that the formation of acetylsulfapyridine stones might have been responsible for an attack of pain, followed by hematuria, which he noted in a patient who was receiving sulfapyridine. Southworth and Cooke²⁷ have described three patients in whom the administration of sulfapyridine led to hematuria accompanied, in two instances, by renal pain and nitrogen retention.

We have observed several patients who developed hematuria in the course of sulfapyridine therapy. One of these is of special interest. The clinical course of this patient, who was ill with type II pneumonia, and sulfapyridine, has already been portrayed in chart 3. It is to be noted that gross hematuria was first observed on the sixth day of treatment. The drug was immediately discontinued. On the next day the hematuria persisted and numerous boat and spearhead-shaped, brownish crystals were noted in the urine. The amount of urine excreted by the patient began to decrease and it was found that the non-protein-nitrogen of the blood was elevated. Over the next 36 hours the degree of hematuria decreased but the blood non-protein-nitrogen gradually increased until the death of the patient.

At autopsy, literally hundreds of small brownish renal calculi were found in both kidney pelves and ureters. These calculi were analysed by Dr. A. C. Bratton of the Department of Pharmacology and were found to contain 0.6 per cent sulfapyridine and 85.6 per cent of acetylsulfapyridine. The melting point of the material found in the stones was 226.8° to 227.8° C. after two recrystallizations from 6 N acetic acid. It was also observed that the melting point was unchanged by the addition of authentic acetylsulfapyridine. Hence, it seemed beyond doubt that these stones were made up mainly of acetylsulfapyridine. Studies of the histological sections of

the kidneys and ureters of this patient did not show abnormalities which could be attributed to stone formation.

Following this observation we have been watching the urine of patients receiving sulfapyridine for the occurrence of acetylsulfapyridine crystals. We have noted that practically all individuals who received the drug had acetylsulfapyridine crystals in their urine. We have been unable to correlate the number of crystals in the urine with the appearance of hematuria. In several patients, despite the presence of great numbers of acetylsulfapyridine crystals in the urine, hematuria, either microscopic or macroscopic, was not detected.

The question of when to stop sulfapyridine therapy in the presence of hematuria has not been settled. We have not discontinued the drug when 10 to 20 red blood cells per high power field appeared in the urine, if the clinical condition of the patients indicated that the drug should be continued. We do believe, however, that macroscopic hematuria is an indication that the drug should be stopped. Acetylsulfapyridine is soluble in alkaline solutions. This suggested the possibility of keeping the urine alkaline (pH 7.5) so that the tendency of acetylsulfapyridine to crystallize out would be diminished. Recently, we have administered bicarbonate of soda to patients who were receiving sulfapyridine. Our experience in this respect is not yet great enough to warrant any statement as to the value of the procedure.

Sulfapyridine and acetylsulfapyridine are excreted slowly, if the kidney function is diminished, and care should be taken in patients suffering from renal disease, that the drug does not accumulate in the body. We have administered sulfapyridine to patients who have grave impairment of renal function and did not note that the drug increased the degree of existing renal damage.

Hepatitis. We have observed one instance of hepatitis associated with jaundice and unaccompanied by acute hemolytic anemia, in a patient who was receiving sulfapyridine.

Disturbances in the Red Blood Cells. Two instances of acute hemolytic anemia occurring within the first five days of treatment have been noted in negroes who were receiving sulfapyridine. Slowly developing anemias seem to be somewhat less common in the course of sulfapyridine therapy than has been noted when sulfanilamide has been prescribed.

Disturbances in the White Blood Cells. We have observed two patients who developed agranulocytosis in the third week of therapy with sulfapyridine. The drug was immediately discontinued in both instances. One patient recovered from this toxic manifestation, and the other died. One patient, in the series of cases reported in this paper, developed a severe leukopenia at the end of the first week of treatment with sulfapyridine. The drug was stopped and the white blood cell count rapidly returned to normal.

COMMENT

The results which we have obtained during the past year from the use of sulfapyridine therapy in pneumococcal pneumonia are confirmatory of the findings of other observers, and support the belief that the drug is of great value in the treatment of pneumococcal infections. Our observations indicate, as do those of other investigators, that the intelligent, widespread use of this drug in pneumonia should result in a marked lowering of the gross mortality rate from this disease.

Sulfapyridine has usually been found to be less readily absorbed and more slowly excreted in human beings than is sulfanilamide. It is distributed in the tissues of the body in a manner somewhat similar to that noted for sulfanilamide. The percentage of sulfapyridine that is conjugated to the acetyl form in the tissues is frequently quite high. The fraction of the drug which is absorbed from the gastrointestinal tract is excreted mainly in the urine in which the drug exists as such, and as acetylsulfapyridine. Because of the variations in the absorption, the excretion and the acetylation of the drug, precise therapy by the peroral route is more difficult with sulfapyridine than it is with sulfanilamide.

The immediate effect of adequate doses of sulfapyridine in pneumonia is to cause a marked fall in the fever. The pulse and respirations return more slowly to normal than does the temperature. The physical signs of the disease may disappear rapidly or they may evolve in a manner similar to that noted in pneumonias of untreated patients. This makes it necessary to continue therapy until convalescence from the disease is well established, for otherwise a relapse of the infection may take place.

It has been possible to use peroral therapy alone in the majority of patients whom we have treated during the past year. However, in patients severely ill with pneumonia, or in those individuals who did not readily absorb the drug following peroral therapy, the intravenous use of the soluble monohydrate sodium salt of sulfapyridine has been a practical and very helpful therapeutic procedure. The toxic manifestations which we have observed in the course of sulfapyridine therapy have been essentially those previously noted in the course of therapy with sulfanilamide. Nausea and vomiting occur much more frequently when sulfapyridine is given. The drug does not cause acidosis. A new toxic manifestation, that of the formation of acetylsulfapyridine renal calculi with the production of pain and hematuria has been observed in the course of sulfapyridine therapy.

CONCLUSIONS

1. During the past year (1938-39) the case fatality rate in 139 adults ill with pneumococcal pneumonia in The Johns Hopkins Hospital was 7.2 per cent. We attribute this low death rate to the use of antipneumococcal serum, sulfapyridine, and serum and sulfapyridine in the treatment of pneumonia.

2. Sulfapyridine has proved to be a valuable chemotherapeutic agent in the treatment of pneumonia.

3. The drug is irregularly absorbed from the gastrointestinal tract in human beings.

4. A relatively large fraction of the sulfapyridine which is absorbed may be conjugated to acetylsulfapyridine.

5. The soluble sodium salt of sulfapyridine which may be given by the intravenous route is a valuable adjunct in the treatment of severe pneumococcal infections.

6. The therapeutic use of the drug in patients ill with pneumonia must be continued until convalescence is established, if relapses are to be avoided.

7. In certain individuals, the administration of sulfapyridine produces toxic manifestations similar to those previously described as occurring in the course of therapy with sulfanilamide.

8. Renal calculi, composed of acetylsulfapyridine, may form in the urinary tracts of patients who are receiving sulfapyridine.

9. The complete abandonment of the therapeutic use of type specific serum in pneumonia is not indicated in the light of our experience.

10. The widespread and intelligent use of the specific therapeutic agents now available for the treatment of pneumonia should cause a sharp drop in the gross mortality rate in this disease.

We are indebted to Lederle, Inc., and E. R. Squibb and Sons for certain of the anti-pneumococcal sera which were used in the treatment of these patients, to Eli Lilly and Company and the Calco Chemical Company, Inc. for the sodium sulfapyridine, and to the Calco Chemical Company, Inc. and Merck and Company for the sulfapyridine.

BIBLIOGRAPHY

1. LONG, P. H., and FEINSTONE, W. H.: Observations upon the absorption and excretion of sulfapyridine, *Proc. Soc. Exper. Biol. and Med.*, 1938, xxxix, 486.
2. MARSHALL, E. K., JR., BRATTON, A. C., and LITCHFIELD, J. T.: The toxicity and absorption of 2-sulfanilamidopyridine and its soluble salt, *Science*, 1938, lxxxviii, 597.
3. BAINES, E. J., and WIEN, R.: The absorption and excretion of 2-sulphanilylaminopyridine, *Quart. Jr. Pharm. and Pharmacol.*, 1939, xii, 4.
4. BRATTON, A. C., and MARSHALL, E. K., JR.: A new coupling compound for sulfanilamide determination, *Jr. Biol. Chem.*, 1939, cxxviii, 537.
5. ANTOPOL, W., and ROBINSON, H.: Urolithiasis and renal pathology after oral administration of 2 (sulfanilylamino)-pyridine (sulfapyridine), *Proc. Soc. Exper. Biol. and Med.*, 1939, xl, 428.
6. GROSS, P., COOPER, F. B., and LEWIS, M. L.: Urinary concretions caused by sulfapyridine, *Proc. Soc. Exper. Biol. and Med.*, 1939, xl, 448.
7. LONG, P. H., and BLISS, E. A.: The clinical and experimental use of sulfanilamide, sulfapyridine and allied compounds, 1939, Macmillan Company, New York City.
8. MARSHALL, E. K., JR., and LONG, P. H.: The intravenous use of sodium sulfapyridine, *Jr. Am. Med. Assoc.*, 1939, cxii, 1671.
9. HOBSON, F. G., and MACQUAIDE, D. H. G.: Treatment of meningococcal meningitis with 2-sulphanilylamidopyridine (M. & B. 693), *Lancet*, 1938, ii, 1213.
10. SCHMIDT, L. H., and HUGHES, H. B.: Absorption and excretion of sulfanilamidopyridine (2-para-aminobenzene-sulphonamidopyridine), *Proc. Soc. Exper. Biol. and Med.*, 1939, xl, 409.

11. EVANS, G. M., and GAISFORD, W. F.: Treatment of pneumonia with 2(p-aminobenzene-sulphonamido) pyridine, *Lancet*, 1938, ii, 14.
12. TELLING, M., and OLIVER, W. A.: Case of massive pneumonia, Type III with massive collapse, treated with 2(p-amino-benzenesulphonamide) pyridine, *Lancet*, 1938, i, 1391.
13. DYKE, S. C., and REID, G. C.: Treatment of lobar pneumonia with M. & B. 693, *Lancet*, 1938, ii, 1157.
14. FLIPPIN, H. F., LOCKWOOD, J. S., PEPPER, D. S., and SCHWARTZ, L.: The treatment of pneumococcic pneumonia with sulfapyridine, *Jr. Am. Med. Assoc.*, 1939, cxii, 529.
15. AGRANAT, A. L., DREOSTI, A. O., and ORDMAN, D.: Treatment of pneumonia with 2(p-aminobenzenesulphonamido) pyridine (M. & B. 693), *Lancet*, 1939, i, 309.
16. BARNETT, H. L., HARTMANN, A. F., PERLEY, A. M., and RUHOFF, M. B.: The treatment of pneumococcic infections in infants and children with sulfapyridine, *Jr. Am. Med. Assoc.*, 1939, cxii, 518.
17. MACCOLL, W. A.: Clinical experience with sulfapyridine, *Jr. Pediat.*, 1939, xiv, 277.
18. CRAWFORD, J. H.: Pneumococcal pneumonia complicating pulmonary tuberculosis, treated with M. & B. 693, *Brit. Med. Jr.*, 1939, i, 608.
19. HODES, H. L., STIFLER, W. C., JR., WALKER, E., McCARTY, M., and SHIRLEY, R. G.: The use of sulfapyridine in primary pneumococcic pneumonia and in pneumococcic pneumonia associated with measles, *Jr. Pediat.*, 1939, xiv, 417.
20. GRAHAM, D., WARNER, W. P., DAUPHINEE, J. A., and DICKSON, R. C.: The treatment of pneumococcal pneumonia with daganan (M. & B. 693), *Canad. Med. Assoc. Jr.*, 1939, xl, 325.
21. MEAKINS, J. C., and HANSON, F. R.: The treatment of pneumococcic pneumonia with sulfapyridine, *Canad. Med. Assoc. Jr.*, 1939, xl, 333.
22. PLUMMER, N., and ENSWORTH, H.: Preliminary report of the use of sulfapyridine in the treatment of pneumonia, *Bull. N. Y. Acad. Med.*, 1939, Second Series, xv, 241.
23. ALSTED, G.: Type III pneumococcal pneumonia, Effect of M. & B. 693, *Lancet*, 1939, i, 869.
24. ALSTED, G.: Behandling Af Pneumonia Med Sulfanilylaminopyridin (M. & B. 693), *Ugesk. f. laeger*, 1939, Nr. xvi, 480.
25. FINLAND, M., SPRING, W. C. JR., LOWELL, F. C., and BROWN, J. W.: Specific serotherapy and chemotherapy of the pneumococcus pneumonias, *ANN. INT. MED.*, 1939, xii, 1816.
26. LAWRENCE, E. A.: Recent advances in the treatment of pneumonia, *Washington Institute of Med.*, 1939, p. 45.
27. SOUTHWORTH, H., and COOKE, C.: Hematuria, abdominal pain and nitrogen retention associated with sulfapyridine, *Jr. Am. Med. Assoc.*, 1939, cxii, 1820.

THE CLINICAL MANIFESTATIONS OF THE VARIOUS TYPES OF RIGHT SIDED HEART FAILURE (COR PULMONALE) *

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ALTHOUGH the interdependence of the several cardiac chambers in the maintenance of efficient circulatory function is acknowledged, it is nevertheless recognized that the various anatomical and physiological disorders which disturb the cardiac function often affect, at least for a time, one side of the heart more than the other; and that in most instances the early clinical manifestations tend to indicate whether the right or the left ventricle is mainly involved. Furthermore, the recognition of the particular side of the heart initially affected often will furnish diagnostic evidence of the underlying pathological process as well as therapeutic indications for the adequate management of the case. The importance, therefore, of an understanding of the features distinguishing right and left ventricular failures, respectively, is apparent. Although a number of contributions have appeared in recent years on the subject of left ventricular failure,^{1, 2, 3, 4} right ventricular failure has received relatively little attention. It is the purpose of this communication to present a résumé of the present day knowledge of the various features of strain and failure of the right side of the heart.

The term "cor pulmonale," originally intended to denote cardiac strain and failure directly due to pulmonary disease, may logically be employed in a broader sense to include all types of cardiac strain and failure in which the right side of the heart is importantly involved, either as the initial circulatory disorder (primary cor pulmonale) or as a consequence of an antecedent failure of the left side of the heart (secondary cor pulmonale).† In the majority of cases the immediate cause is an obstruction or increased

* Received for publication July 15, 1938.

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† The term "cor pulmonale" may be construed as signifying that the immediate cause of the cardiac disorder is a lesion disturbing the pulmonary circuit. Such a lesion may be located at any point between the mouths of the venae cavae on the right side of the heart and the mitral orifice on the left. Cor pulmonale in this sense would therefore include all instances of cardiac strain in which the right side is involved on the basis of pathological anatomy or physiology peculiar to that side. However, "cor pulmonale" cannot logically include right sided heart failure occurring simultaneously with failure of the left side of the heart brought about by conditions affecting the heart as a whole, as exemplified by the cardiopathies of hyperthyroidism, acute myocarditis, myxedema, anemia, beri-beri, prolonged paroxysmal tachycardia, and functional persistent auricular fibrillation. In some of these instances, particularly in the beri-beri heart, evidence of right sided heart failure (congestion of the systemic veins and liver) may predominate over pulmonary engorgement; and although the heart as a whole is much enlarged, the dilatation of the right auricle and ventricle as well as of the pulmonary artery may appear especially prominent in the roentgenogram.⁵ This may be due to the lesser reserve of the musculature of the right chambers, or as suggested by Aalsmeer and Wenckebach,⁶ to the fact that the left ventricle is functionally spared by the greatly reduced output of the right ventricle.

resistance to the blood flow within the lesser (pulmonary) circuit at any point between the pulmonary conus and the mitral valve. In a few instances, in the absence of direct obstruction, right sided strain and failure

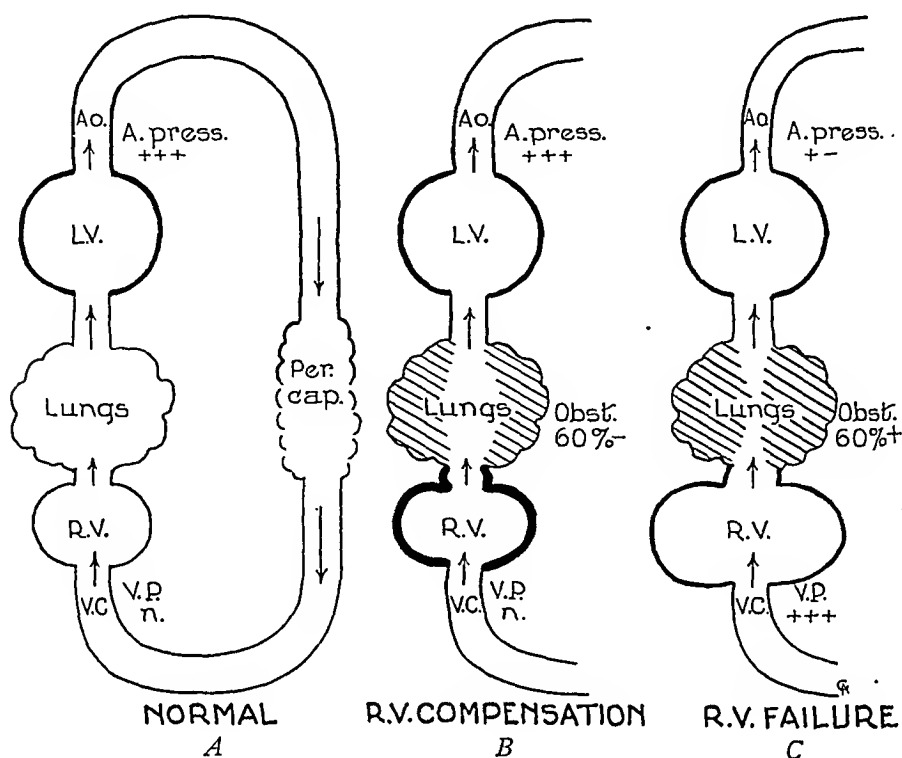


FIG. 1. Schematic drawing showing the mechanism of production of cor pulmonale in the stages of compensation and failure. *A.* Normal circulation. *B.* Strain of right ventricle due to obstruction of pulmonary vascular bed (less than 60 per cent). Hypertrophied right ventricle is shown in stage of compensation. The pulmonary resistance is successfully overcome and adequate ventricular output is maintained with normal systemic arterial and venous pressures. At this stage there may be no symptoms except roentgenographic evidence of dilatation of the pulmonary conus. *C.* Stage of decompensation (right ventricular failure). Pulmonary vascular narrowing exceeds 60 per cent, a degree of obstruction in excess of that for which the average right ventricle is able to compensate. The right ventricle is shown dilated with diminished ventricular output, low aortic pressure and increased systemic venous pressure.

may result from increased right ventricular output such as occurs in congenital septal defects and in organic tricuspid regurgitation.

THE GENERAL SYMPTOMS AND SIGNS OF COR PULMONALE

The symptoms and signs of cor pulmonale are of two categories: The first comprises the manifestations of the antecedent or associated cardiopulmonary disease; the second includes the disturbances produced directly by the hypertrophy, dilatation and failure of the right cardiac chambers.

I. The manifestations of the underlying cardiopulmonary disease are (1) cyanosis, (2) dyspnea, (3) polycythemia, (4) hemoptysis, (5) clubbing of the fingers and toes, and (6) the specific signs and symptoms of

the particular disease present, such as chronic bronchitis, emphysema, pulmonary fibrosis and other similar lesions.

II. The disturbances arising directly from the strain and failure of the right cardiac chambers are (1) increased venous pressure affecting the territories of both venae cavae and resulting in (a) engorgement of the superficial veins, (b) subcutaneous edema, (c) visceral congestion with palpable enlargement and tenderness of the liver, (d) transudation into the serous cavities, (e) oliguria with albumin and sometimes blood due to passive congestion of the kidneys, and (f) increased cerebrospinal pressure; (2) hypertrophy and dilatation of the right auricle, right ventricle and conus and dilatation of the pulmonary artery which are demonstrated most readily by roentgen-ray examination and often also by palpation (lower sternal

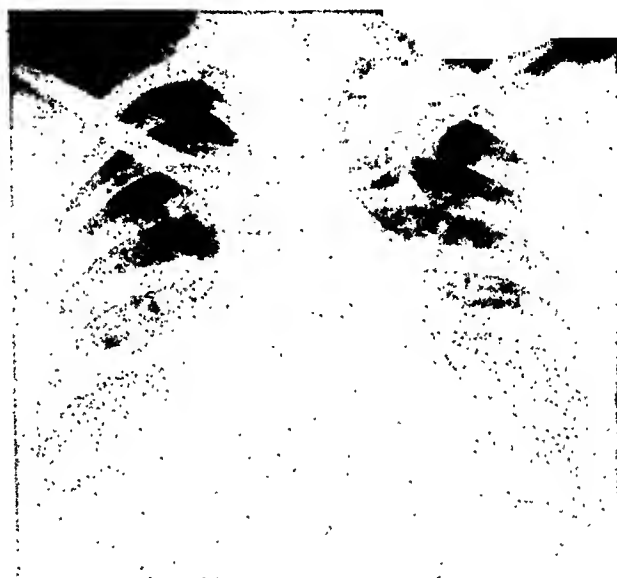


FIG. 2. Roentgenogram showing cardiac silhouette characteristic of cor pulmonale. Bulge in the region of the cardiac waist ("filling" of waist) is due to dilatation of pulmonary artery and conus.

thrust) and percussion (filling of waist); (3) accentuated pulmonic second sound and the presence in the left second and third interspaces of murmurs, thrills, and gallop rhythm; and (4) low systemic blood pressure.

The electrocardiogram often reveals right axis deviation. However, the hypertrophy of the right ventricle may be counterbalanced by an equal degree of left ventricular enlargement in which case no ventricular preponderance occurs. In some instances left axis deviation is encountered when the hypertrophy of the left ventricle exceeds that of the right.

PRIMARY COR PULMONALE

Although occurring less frequently than the secondary variety (the ratio being about one to five), primary cor pulmonale is symptomatically

the more important, since it is only in this type that the classical picture of isolated right sided heart strain is observed. From the standpoint of the clinical course as well as etiology there are recognized three subdivisions of primary cor pulmonale, the acute, the subacute, and the chronic.

Acute Cor Pulmonale.^{7, 8} Acute cor pulmonale results from a sudden obstruction of the trunk or first branches of the pulmonary artery * by embolism or (rarely) by rapid thrombosis.⁹ The onset is explosive with extreme suffocating dyspnea, cyanosis and often pain. The pain may be in the sternal region, on either side of the chest, or in the shoulders. In addition there are usually symptoms of severe shock, and (rarely) convulsions or coma may be present.

The objective findings are those of severe shock and, if the patient survives the initial attack, of strain and failure of the right side of the heart. There is a deep, almost black, cyanosis or an ashy paleness and profuse perspiration. The pulse is rapid and very weak. The blood pressure is low. Dilatation of the pulmonary artery and conus may be demonstrable by percussion, palpation, or by the roentgenogram. The second pulmonic sound is frequently accentuated and a gallop rhythm may be present. Occasionally a pericardial friction rub may be heard with maximal intensity in the region of the left second, third and fourth interspaces. The lungs may show nothing abnormal, but often râles are present. Less frequently fluid may be found at the bases, and occasionally widespread pulmonary edema may develop. Fever and leukocytosis are often present.

The clinical picture of acute cor pulmonale strongly resembles that of acute coronary occlusion. During the first 12 to 24 hours the differential diagnosis is often extremely difficult. Pain is more apt to dominate the picture of coronary occlusion, dyspnea that of pulmonary embolism. McGinn and White⁷ noted the following electrocardiographic changes which they regard as characteristic of acute cor pulmonale: "The presence of a Q-wave and late inversion of the T-wave in Lead III, the rather low origin of the T-wave with a gradual staircase ascent of the ST interval in Lead II, a prominent S-wave and a slightly low origin of the T-wave in Lead I, and an upright T-wave (with inverted P and QRS waves) in Lead IV." In some of their cases there was definite right axis deviation. In none was left axis deviation present at the time of the acute episode. These electrocardiographic changes are temporary and usually disappear within 48 hours after the attack.

The prognosis is grave, the mortality being in excess of 50 per cent; most of the fatal cases die within 30 minutes to 24 hours after the occlusion. However, the patients who survive usually make a complete recovery.

Treatment^{10, 11} consists of the immediate administration of antispasmodic substances, such as papaverine (one-half grain intravenously) or atropine, and enough morphine to control pain. Oxygen is indicated in the

* In rare instances emboli involving the minute branches or the capillaries may be so numerous as to produce acute right ventricular failure similar to that resulting from an obstruction of the primary branches.⁵

presence of cyanosis and dyspnea. Embolectomy¹² by the Trendelenburg operation^{13,14} has been attempted and in rare instances has proved successful. However, as yet, this procedure must be viewed as strictly experimental.

Since the most common cause of pulmonary embolism is venous thrombosis in the lower extremities,* prevention of the latter becomes a matter of prime importance. Factors favoring venous thrombosis are circulatory stasis, dehydration and trauma. Such conditions are most apt to develop in persons of relatively advanced years as a result of surgical operations (especially abdominal or pelvic) or accidents. Circulatory insufficiency is an important contributing factor. The following preventive measures are recommended by Barnes¹⁰ for postoperative cases, especially for patients more than 40 years of age: "The patient is placed in the Trendelenburg position for the first 24 hours after operation. Carbon dioxide is administered by inhalation several times in the day and night for the first 48 hours. Frequent deep breathing exercises are urged in every case. Attempts at early coughing are encouraged as much as possible. Extreme care is observed to keep the patient's legs warm at the operation, during his transfer to his room, and after his return to bed. Frequent massage of the legs is practiced during the first 48 hours and twice daily thereafter until the patient is out of bed. Passive and active movements of the extremities are insisted on at stated intervals from the time the patient is returned to his room until he is out of bed." Prolonged recumbency should be avoided and adequate measures employed to combat circulatory failure. Desiccated thyroid may be administered cautiously in suitable cases to increase the velocity of the venous return.

Many of these measures are also applicable to medical cases in which prolonged inactivity is necessary.

Subacute Cor Pulmonale. Subacute cor pulmonale is characterized by the rapid development of signs and symptoms of right ventricular strain in a patient who gives no history of antecedent cardio-pulmonary disease or of any other condition known to be capable of producing strain of the right side of the heart. Cases belonging to this group have been reported by Schmidt,¹⁵ Krutzsch,¹⁶ Greenspan,¹⁷ and Brill and Robertson.¹⁸ The latter authors recently have summarized the clinical and pathological features of this rare condition and suggested the term "subacute cor pulmonale" as most descriptive of its clinical manifestations. The cause is a rapidly progressive narrowing and obliteration of the pulmonary vascular bed by a metastatic carcinomatous invasion of the pulmonary lymphatics and arterioles. The process of vascular narrowing is further accelerated by secondary intimal connective tissue proliferation and thrombosis (carcinomatous lymphangitis and endarteritis).

*The veins of the gastrocnemius and soleus muscles are frequently found to be the seat of such thrombosis and the source of pulmonary embolism. This observation originally made by Erdheim (Vienna) has been amply confirmed in our clinic.

The dominant symptoms are dyspnea and unproductive cough, which, though mild at the onset, tend to progress rapidly, and after continuing with increasing severity for two weeks to two months (rarely longer) end fatally. Death occurs more or less suddenly with symptoms of circulatory collapse and signs of acute right heart failure.

This syndrome is distinguished from the acute cor pulmonale by the more gradual onset without pain or shock and by the relatively more prolonged and progressive course. It is differentiated from the chronic types of cor pulmonale by the absence of antecedent cardio-pulmonary disease and by the much shorter course than is usual in the chronic types. In the latter the duration of the cardio-pulmonary symptoms varies from six months to more than five years with an average duration of two years.

So far as is now known, metastatic carcinoma is the only pathological process which is capable of producing the clinical picture of subacute cor pulmonale. In most of the reported cases the primary lesion was a scirrhus carcinoma of the stomach. The patients were all relatively young subjects 36 to 40 years of age. Some gave a history of "peptic ulcer," others complained of but vague gastric discomfort for a period of several months to one year or longer. In most instances the primary lesion and the nature of the cardiac strain remained unsuspected during life.

It is possible that cases represented by this clinical syndrome occur more frequently than might be inferred from the foregoing account. In recent reviews Wu¹⁹ and Jarcho²⁰ each collected from the literature a large number of cases of carcinomatous lymphangitis involving the pulmonary vascular bed in a manner capable of producing the picture of subacute cor pulmonale. Although in most of these the involvement of the heart clinically was not mentioned, the symptoms recounted in a number of the quoted reports suggest the possibility that in some of those cases the full picture of subacute cor pulmonale might have been present.

Chronic Primary Cor Pulmonale. Chronic primary cor pulmonale is of manifold etiology. The most important causes are mitral stenosis, extensive pulmonary fibrosis (on the basis of pneumoconiosis, tuberculosis or other chronic infections), and severe emphysema secondary to asthma, chronic bronchitis or some other pulmonary disease. Less frequent causes are marked deformity of the chest (kyphoscoliosis) and certain congenital cardiac lesions; namely, defects of the pulmonary valve, patent ductus arteriosus and septal defects. Still rarer causes are organic tricuspid regurgitation and primary pulmonary arteriosclerosis.

The clinical manifestations are those enumerated in the earlier part of the paper as "the general symptoms and signs of cor pulmonale." In the early stages, before actual cardiac failure supervenes, only the symptoms and signs related to the associated cardio-pulmonary pathology may be present, and the involvement of the right ventricle may be difficult to demonstrate except by roentgenographic disclosure of the dilatation of the pulmonary artery and conus. With the onset of right ventricular failure the classical picture

of chronic cor pulmonale becomes complete. The grouping of the symptoms and their severity will depend upon the type and extent of the underlying cardio-pulmonary disease. In cases of long-standing with diffuse lung involvement including pulmonary vascular sclerosis and hypertension, there sometimes develops an extreme, almost black cyanosis ("cardiacos negros" of Ayerza and Arrillaga²¹), along with the entire picture of chronic cor pulmonale described above, including also cerebral manifestations (headache, mental confusion and somnolence) and attacks of severe anginal pain, radiating deeply toward the back (hypercyanotic angina). This syndrome, sometimes referred to as Ayerza's disease, represents merely an extreme degree of chronic cor pulmonale which may arise from any of the etiologic factors enumerated above when severe enough to produce extensive pulmonary arteriosclerosis with hypertension and marked narrowing of the pulmonary vascular bed.

The course of chronic primary cor pulmonale is progressive but slow, extending over a period of years. Most of the patients die of an intercurrent infection, especially pneumonia; some die of congestive heart failure; a few die either suddenly or in acute circulatory collapse similar to that which often is observed in the acute and subacute types of cor pulmonale. In this latter mode of death the patient while apparently comfortable, suddenly becomes breathless and panicky. The pulse becomes rapid and weak. Death occurs usually within one to several hours. As was pointed out in a previous communication¹⁸ the sudden circulatory collapse probably represents a stage in the obstructive pulmonary process in which the narrowing of the pulmonary vascular bed reaches a degree beyond that compatible with life (more than 60 per cent narrowing). At such a high degree of pulmonary vascular obstruction, due to the marked reduction in the right ventricular output and consequent lowering of the aortic pressure, a diminished coronary flow occurs which causes further weakening of the right ventricle. A vicious circle is thus established resulting either in instant death (perhaps due to failure of the cardiac pacemakers²²) or in acute circulatory collapse with death in a few hours.

The treatment of chronic cor pulmonale consists of the management of the underlying pulmonary disease and of the myocardial insufficiency when present. The treatment of the latter includes the usual measures for congestive failure, namely, rest, dietary restriction, digitalis and diuretics. Oxygen is indicated in the presence of dyspnea or cyanosis whether of cardiac or of pulmonary origin. Additional therapy for the underlying pulmonary disease will be determined, of course, by the specific disturbance present. In many instances the pathological process is irreversible and little can be expected from this part of the treatment. However, in all cases digitalis and diuretics should be tried; much relief is often obtained by the removal of occult edema, even if no visible congestion is present.

SECONDARY COR PULMONALE

Although the most common type of right sided heart failure,²³ secondary cor pulmonale, for the purpose of this discussion, requires little special consideration, since it merely represents an advanced stage of general heart failure. The immediate cause of secondary cor pulmonale is the pulmonary congestion and consequent increased resistance to the pulmonary circulation resulting from an antecedent failure of the left ventricle.

The remote causes of secondary cor pulmonale are the conditions which are commonly responsible for failure of the left side of the heart. The most important of these are (1) hypertensive disease, (2) deformities of the aortic valve, and (3) coronary artery disease. The latter, although affecting the heart as a whole, usually involves the left ventricle to a greater extent than the right, and symptoms of pulmonary congestion (dyspnea, continuous or paroxysmal, diminished vital capacity, etc.) which are pro-

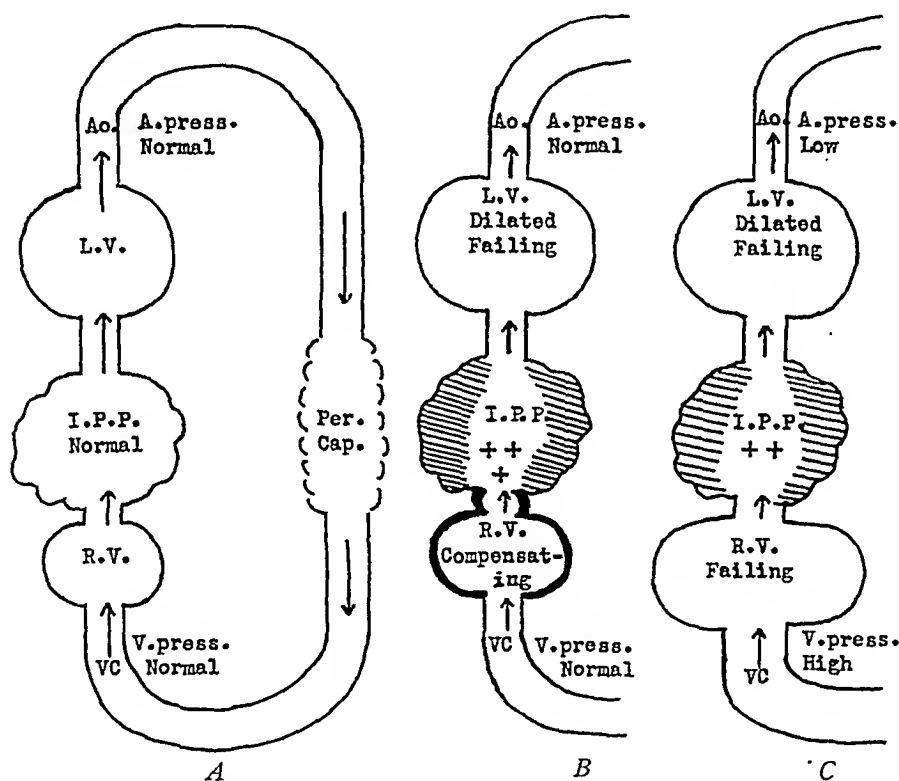


FIG. 3. Schematic drawing showing the mechanism of production of right ventricular failure secondary to failure of the left ventricle (secondary cor pulmonale). A. Normal circulation. B. Strain of the right ventricle in the stage of compensation. The strain is due to the increased intrapulmonary pressure resulting from failure of the left ventricle. The aortic pressure, however, remains normal or only moderately lowered and the systemic venous pressure likewise remains normal as long as the hypertrophied right ventricle is compensating and its output continues at normal or above normal levels. The increased intrapulmonary pressure is responsible for the accentuated second pulmonic sound noted clinically. C. Finally the right ventricle dilates and fails; the systemic venous pressure becomes greatly increased (resulting in peripheral edema noted clinically), and the aortic pressure is significantly lowered. There is also a moderate lowering in the intrapulmonary pressure which sometimes results in a slight improvement in the dyspnea.

duced by failure of the left ventricle often precede the appearance of symptoms due to failure of the right ventricle (peripheral edema, congestion of the liver and distention of the superficial veins). In most of these instances but a short time (hours, days, or weeks) elapses between the onset of left ventricular failure and the first manifestations of failure of the right side of the heart. On the other hand in hypertensive disease and in some cases of aortic disease, symptoms of left ventricular failure may prevail over a more extended period before signs of right sided heart failure become manifest. Not infrequently breathlessness or attacks of paroxysmal dyspnea continue for years and death occurs either during such a paroxysm or as a result of a complicating coronary thrombosis without peripheral edema ever making its appearance. In some instances, the onset of failure of the right ventricle results in an improvement of the pulmonary congestion with consequent relief of breathlessness and disappearance or lessening in the frequency of attacks of paroxysmal dyspnea.

The treatment consists of the standard measures employed in congestive failure, including rest, digitalis, dietary restriction, diuretics, venesection and oxygen. The prognosis depends largely upon the underlying condition responsible for the left ventricular failure. In syphilitic aortic disease, after congestive failure is well established, but little temporary benefit can be secured from any mode of therapy, and death may be expected within one to two years. On the other hand in cases of essential hypertension without significant renal involvement extremely gratifying results can be obtained from the judicious application of the aforementioned therapeutic procedures, and relatively good health may be maintained over a period of years.

REFERENCES

1. WEISS, S., and ROBB, G. P.: Cardiac asthma (paroxysmal cardiac dyspnea) and the syndrome of left ventricular failure, *Jr. Am. Med. Assoc.*, 1933, c, 1841.
2. WHITE, P. D.: Weakness and failure of the left ventricle without failure of the right ventricle: Clinical recognition, *Jr. Am. Med. Assoc.*, 1933, c, 1993.
3. HARRISON, T. R.: Failure of the circulation, 1935, Williams & Wilkins Company, Baltimore, p. 6.
4. SMITH, F. M.: Treatment of left ventricular failure, *Jr. Am. Med. Assoc.*, 1937, cix, 646.
5. FISHBERG, A. M.: Heart failure, 1937, Lea & Febiger, Philadelphia, p. 557.
6. AALSMEER, W. C., and WENCKEBACH, K. S.: Herz und Kreislauf bei der Beri-beri-Krankheit, *Wien. Arch. f. inn. Med.*, 1929, xvi, 193. Cited by Fishberg.⁵
7. MCGINN, S., and WHITE, P. D.: Acute cor pulmonale resulting from pulmonary embolism, *Jr. Am. Med. Assoc.*, 1935, civ, 1473.
8. WHITE, P. D.: The acute cor pulmonale, *ANN. INT. MED.*, 1935, ix, 115.
9. FOWLER, W. M.: Obliterating thrombosis of the pulmonary arteries, *ANN. INT. MED.*, 1934, vii, 1101.
10. BARNES, A. R.: Pulmonary embolism, *Jr. Am. Med. Assoc.*, 1937, cix, 1347.
11. EDITORIAL: Pulmonary embolism, *ANN. INT. MED.*, 1938, xi, 1506.
12. SHAMBAUGH, PHILIP: Pulmonary embolectomy, *Ann. Surg.*, 1936, civ, 823.
13. NYSTRÖM, G.: Experiences with the Trendelenburg operation for pulmonary embolism, *Ann. Surg.*, 1930, xcii, 498.

14. WESTERBORN, A.: Trendelenburg's operation for pulmonary embolism. Report of recent additional case, *Ann. Surg.*, 1931, xciii, 816.
15. SCHMIDT, M. B.: Die Verbreitungswege der Karzinome und die Beziehung generalisierter Sarkome zu den leukämischen Neubildungen, Jena, Gustav Fischer, 1903.
16. KRUTZSCH, G.: Über rechtseitige Herzhypertrophie durch Einengung des Gesamtquerschnittes der kleineren und kleinsten Lungenarterien, *Frankfurt. Ztschr. f. Path.*, 1920, xxiii, 247.
17. GREENSPAN, E. B.: Carcinomatous endarteritis of the pulmonary vessels resulting in failure of the right ventricle, *Arch. Int. Med.*, 1934, liv, 625.
18. BRILL, I. C., and ROBERTSON, T. D.: Subacute cor pulmonale, *Arch. Int. Med.*, 1937, lx, 1043.
19. WU, T. T.: Generalized lymphatic carcinosis ("lymphangitis carcinomatosa") of the lungs, *Jr. Path. and Bact.*, 1936, xliii, 61.
20. JARCHO, S.: Diffusely infiltrative carcinoma. A hitherto undescribed correlation of several varieties of tumor metastasis, *Arch. Path.*, 1936, xxii, 674.
21. ARRILLAGA, F. C.: Sclérose de l'artère pulmonaire, *Bull. et mém. Soc. méd. d. hôp. de Paris*, 1924, xlviii, 292.
22. FINEBERG, M. H., and WIGGERS, C. J.: Compensation and failure of the right ventricle, *Am. Heart Jr.*, 1936, xi, 255.
23. THOMPSON, W. P., and WHITE, P. D.: The commonest cause of hypertrophy of the right ventricle—left ventricular strain and failure, *Am. Heart Jr.*, 1936, xii, 641.

SOME PROFESSIONAL AND SOCIAL TRENDS IN AMERICAN MEDICINE*

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It is a matter of difficulty, if the task be not wholly impossible, for the individual worker in any field of medical practice correctly to evaluate the multitudinous changes which are constantly occurring in this field of human endeavor. It is but a comparatively short time since didactic instruction compassed the training for a career in medicine and the armamentarium of the doctor consisted of a thermometer, a stethoscope, an obstetrical bag and a few instruments. The increase in medical knowledge during the present century has been so vast and the changes in social, economic and scientific aspects of modern civilization have progressed so rapidly as to demand a complete reorientation for an appreciation of their significance and implications. While the physician remains an individualist so far as the application of curative medicine is concerned, he cannot remain oblivious to other important elements in our social fabric since the problems of illness which he solves for the individual have an interest for the community as a whole, particularly in their preventive and social aspects. This changed conception of professional obligation has brought to the fore many problems, the solution of which is not yet in sight, but which demand our earnest consideration and study. In order that I may confine my remarks to something approaching a logical order of sequence, my subject will be discussed under two headings, scientific and social trends.

SCIENTIFIC TRENDS

Having been reared professionally in the waning shadow of one school of thought, that founded on clinical observation alone, and in this golden age seeing the beautiful fruition of that built on accurate scientific knowledge, I can but pay in an inadequate manner a feeble tribute to the votaries of science in bringing about this transformation and increasing the sum total of human knowledge. This accretion has followed three pathways, first the anatomical, second the pathological, and today the physiological and biochemical. "The most significant trend of surgery has been the attempt to control, ameliorate, abort and prevent those condition which are known or suspected to be dependent on disturbed physiological processes." This is notably true in the surgery of the sympathetic nervous system with the control of vasomotor spasm, the surgery of peptic ulcer, in the surgical treatment of conditions dependent on abnormal activity of the ductless glands and in the collapse therapy of pulmonary tuberculosis. Many factors for the safety of surgical patients have been developed in the preoperative

* Read at the New Orleans meeting of the American College of Physicians, March 27, 1939.

care, the technical procedure and the postoperative care with a consequent reduction in mortality of appreciable degree. The exact tests evolved in the clinical and experimental laboratories, of which there are many, when intelligently correlated with the history and physical findings, permit of greater accuracy in diagnosis and prognosis and of greater exactitude in therapy than ever known before. The many agents for inducing anesthesia, with or without the employment of synergistic drugs, allow a selection of the one best suited to the patient and the disease, while contributing materially both to comfort and safety. The brilliance of the accomplishments in the highly specialized fields of surgery is but enhanced by the former belief that they were unattainable. Thoracic surgery now offers repair of cardiac wounds, pericardiectomy in Pick's disease, an experimental effort to supplement coronary circulation, pneumonectomy in whole or in part for the relief of bronchiectasis and tumor, and collapse therapy for pulmonary tuberculosis by means of intrapleural pneumolysis, extrapleural apicolysis, interruption of the phrenic nerve and thoracoplasty partial or complete. Neurosurgery successfully ventures the exploration of the innermost recesses of the brain for the relief of pressure and the removal of tumors, even daring the ablation of a lobe or of an entire hemisphere. Sympathectomy finds an ever widening field of usefulness in correcting disorders dependent upon perverted nerve function and impeded vascular channels. The era of speed and the removal of large portions of the body to get rid of a small diseased part has been superseded by a careful meticulous technic which sacrifices no healthy tissue and considers every cell valuable unless diseased. The trend toward the preservation of healthy tissue is well illustrated by the employment of irradiation in the therapy of certain neoplasms, both benign and malignant. Well established major surgical procedures have been abandoned in the search for simpler methods which will reduce mortality and morbidity as instanced in the transurethral resection of the prostate and the injection of sclerosing substances in various conditions. Chemical research is responsible for much of the changing order in medicine. It has altered our conceptions of the physical structure of living tissue, has shown the chemical changes which take place in the discharge of body and organ functions, and increased our knowledge of the chemical substances which may control such activities. The relation of the diseases of metabolism and nutrition to vitamin deficiency and hormonal dysfunction, the rôle of the pancreas in carbohydrate metabolism, of the liver and stomach in hematopoiesis, of the hypophysis in influencing growth and obesity, and of the thyroid in influencing metabolism are beautiful illustrations of the knowledge garnered by this type of research. Increasing knowledge of the endocrine hormones is opening up a field for study and therapy which, if one may venture a prophecy, is but in its infancy. Pneumonia for the first time in its history is being made to give ground by accurate typing and appropriate sera. Modern medical thought with relation to the infectious diseases is first directed toward prophylaxis. Failing

this ideal, a specific remedy, either chemical or biologic, is sought. The present wave of sulfanilamide therapy evinces the eagerness with which the profession awaits any chemical or serum purported to possess specific properties. The fact that heart disease after the age of 40 is the leading cause of death has focused attention on its prevention, early detection and proper treatment. It is interesting to note that total thyroidectomy is being practiced in congestive heart failure with the idea of lessening metabolism and thus decreasing the cardiac load, another instance of the physiological approach to the solution of medical problems. Psychiatry throughout the past century has been a veritable "terra incognita": only when the injunction, "sit lux" of modern science was applied to it has it emerged from the gloom and darkness with which it was enshrouded. Hospitals staffed by competent medical personnel, registered nurses, and aides versed and trained in psychiatry are meeting the challenge of the disordered mind with an orderly mind skilled in the application of scientific, psychiatric knowledge.

One of the most significant trends is to be found in preventive medicine. While the major responsibility in this field devolves upon the United States Public Health Service and the State and County Health Officers, the physician in practice has come to a realization that his obligation to society demands an extension of activity far beyond the intimate personal relationship between the individual patient and himself to the broader field of preventive medicine, widening his sphere of responsibility from the care of patients to that of the community of which the patients are a part. An interested lay public participates in this program through many worthwhile organizations. Legal enactments permitting sterilization of the unfit and requiring a clean bill of health on the part of those who would enter the marriage state, while more specifically in the field of eugenics, give further evidence of lay interest. It has been truly said that preventive medicine forms the keystone of the triumphal arch of modern civilization since the prevention of disease, and therefore the prevention of suffering and death, is a more important and glorious achievement than the cure of the individual or the reduction of disease mortality. A noteworthy accomplishment, largely attributable to prevention, has been the increase in life expectancy which now stands at 62 years. But this indicates that we are slowly developing a society in which old age with its degenerative lesions will represent a constantly increasing percentage of disease.

SOCIAL TRENDS

In the changing social thought of the last few years much has come about that is at wide variance with what heretofore had been regarded as fixed and established. Industrial disability compensation, unemployment compensation and old age pensions are illustrative answers to the biblical question, "Am I my brother's keeper?" With the present urge to procure a greater distribution of social justice, there is in some quarters a tendency to go to the extreme of complete socialization, in which effort medicine

has been selected as a proving ground. If human intelligence and scientific medical knowledge could be dispensed in boxes and crates as a market commodity, its distribution could be fitted into such a concept of economics. The fundamental concept in both ethics and economics is that of value. In economics the ultimate test of value is the amount of goods which will be consumed or the medium of exchange which will be paid in the market. Ethics embraces a wider conception and makes its ultimate test of value the effect on the individual and the society in which he lives. If medical relations are to be ethical—that is, in furtherance of the ultimate good of the patient and of the public welfare—they must be between the patient who is to be treated and the physician trained according to established standards and having access to the accumulated knowledge of the ages. The advances in the distribution of medical knowledge during the past 50 years have been evolutionary, developing means to meet needs as they have arisen. The record is one of which to be proud; mortality has been reduced 50 per cent and life expectancy has been increased 100 per cent. During 1938 an all time low has been attained in the mortality of every disease other than heart disease and cancer. The explanation for their increased mortality becomes readily apparent when we bear in mind the number of people now living in the age groups above 40 years, the period in which these diseases exact their greatest toll. Even with this remarkable accomplishment of American medicine, no agency knows better than the medical profession of the lag or gap that exists between accumulated medical knowledge and its equable distribution. And no agency is more interested in bridging this gap, granting that it be done in a way to maintain the ethical institutions of Medicine. As far back as 1875 the House of Delegates of the American Medical Association recommended the formation of a Department of Health with a cabinet officer at its head, to the end that all health activities might be coördinated and correlated. During the passing years it has repeatedly urged consideration of this proposal. During the same years there has been an increase in participation of governmental agencies in health activities scattered through many departments, the Public Health Service in the Department of the Treasury, Maternal and Child Welfare in the Department of Labor, Food and Drugs in the Department of Agriculture, the care of the Indians and the insane in the Department of the Interior, the care of the Army and Navy in their own Departments, the care of the veterans in the Veterans' Bureau, the care of the indigent farmers in the Resettlement Administration, and so on through more than 20 different agencies involving the expenditure of many millions of dollars. The President of the United States appointed an Interdepartmental Committee to Coördinate the Health and Welfare Activities of the Government, which in turn appointed Technical Committees to assist in the study of its problems, one of which devoted its activities to the study of Medical Care. The National Health Survey, upon which some of its conclusions were based, was a spot survey made largely by WPA workers covering four

million rural and urban inhabitants in 17 states. By using the findings of this survey as an index to the needs of the country as a whole, the Technical Committee assembled data and reached conclusions that in many instances are at variance with the data and information collected by the American Medical Association. If it be true that one-third of the population is poorly clothed, poorly housed, poorly fed and without medical care, the problem presented thereby is even more social and economic than medical. The maternal death rate among the whites compares favorably with that of any other country, while that among the negroes is inordinately high. Many of the negroes live in squalor, are poorly clothed, poorly housed, undernourished and rachitic, and without medical care even though it is often available: that such conditions exist is an indictment of society but certainly not of the medical profession. The availability of hospital service is another feature upon which there is a rather marked discrepancy. But regardless of its errors the report contains factual data upon which all agree and which form a basis for the consideration and study of all agencies in formulating a program for the wider distribution of medical care. In July 1938 a National Health Conference was held in Washington under the auspices of the Interdepartmental Committee at which recommendations for a National Health Program were proposed, envisaging a comprehensive participation by the federal government in health activities. Briefly, the program provided for an expansion of public health service and of maternal and child welfare; expansion and construction of hospital facilities and diagnostic centers; medical care for the medical needy; aid to the states in developing plans for medical care on a tax-paid or compulsory insurance basis; and payments to the worker for disability resulting from sickness. The development of the proposed program was to be a gradual one with completion in 10 years, at which time it would involve an expenditure of \$850,000,000 annually. At a special meeting of the House of Delegates of the American Medical Association held in September 1938, approval was given to expansion of public health service and maternal and child welfare where need could be shown; approval to hospital and diagnostic center construction where need could be shown, recommending, however, utilization of existing facilities to the utmost; approval of medical care to the indigent and medically indigent where need could be shown; approval of the principle of assistance to the worker for temporary disability resulting from illness; approval of group hospitalization and voluntary insurance. But there was unqualified disapproval of tax-paid or compulsory sickness insurance. The special committee appointed by the House of Delegates held two conferences with the Interdepartmental Committee, one on October 31 and one on January 15. Since the Interdepartmental Committee did not at either sitting submit a draft of the proposed legislative enactment for the translation of its recommendations into activity, the discussions were of necessity limited to principles. There was agreement in principle on the objectives of four of the recommendations but disagreement on Recom-

mendation IV which provides federal help for the states initiating studies and plans for the care of all their people on a tax paid basis. Compulsory sickness insurance is a more appealing and euphonious title than the one which accurately identifies it, namely, sickness tax. Mr. Falk of the Technical Committee set the income level at which compulsory plans would operate at \$3000.00 or less. Federal statistics reveal that but 7 per cent of the population enjoy an income above this amount! If and when a compulsory plan becomes operative in all the states at this level, 93 per cent, or 120,000,000 of the population will be covered thereby. On January 23 the President presented to the Congress his message on the National Health Program with a recommendation for its careful consideration and study. On February 28 Senator Wagner of New York introduced into the Senate of the United States a bill, S. 1620, entitled "A bill to provide for the general welfare by enabling the several states to make more adequate provision for public health, prevention and control of disease, maternal and child health services, construction and maintenance of needed hospitals and health centers, care of the sick, disability insurance and training of personnel." Although the bill is actually an amendment to the Social Security Act, the bill proposes that if it is enacted it be called the "National Health Act of 1939." Assuming that this bill has the endorsement of the federal agencies responsible for the National Health Program, it has afforded opportunity to study the means by which it proposes to put into effect the recommendations of the Interdepartmental Committee and by comparison to see how far it harmonizes with the approval in principle given by the House of Delegates at its special session. The American Medical Association at no time expressed its opinion upon the amounts of money to be expended in such a program but it is of interest to note that the Wagner Bill proposes an expenditure of \$98,250,000 for the fiscal year of 1940, \$123,500,000 for the fiscal year of 1941, and \$334,000,000 for the fiscal year of 1942 with no limit in the amounts during 1941 and 1942 for public health work, for grants for mental and tuberculous hospitals, for grants for medical care, for grants for temporary disability compensation, and for administration: and further that for the fiscal years subsequent to 1942 there is no specified limit for expenditure for the accomplishment of any of the purposes of the Act. While no specific mention is made of compulsory sickness insurance, the measure introduces the principle of allotment of federal money to the individual states for medical care, by the Social Security Board, without specifying the means to be used in the individual states for providing such service other than to demand the approval of the Social Security Board, being silent as to the permissible extensions and improvements of medical care that a state may make and as to whether such care shall be provided through a state medical service, or by a system of state health insurance, or by payment for services on a fee basis. The American Medical Association has at no time suggested an administrative agency for the National Health Program but has stressed

its opinion that such be developed within state agencies and state medical bodies. The Wagner Bill specifies three administrative agencies, the Children's Bureau, the United States Public Health Service, and the Social Security Board with final full authority resting in each. The advisory councils mentioned in the bill are vague as to their membership, their duties and their responsibilities. Granting the occurrence in a rural or isolated community of diseases, which from their classification would come under each and all three of these proposed agencies, satisfactory and competent administration would seem extremely difficult if not impossible. Such a contingency is another argument in support of the contention of the American Medical Association that a Secretary of Health, a unified agency for the correlation of all health activities is a necessity. The bill does not provide for means of determining the local need for the various services it proposes to furnish, a matter of importance repeatedly emphasized by the House of Delegates. No stipulation is made as to the utilization and improvement of existing hospitals in the face of the fact that the hospitals of this country constantly show a 30 per cent bed vacancy. These are some of the points that demand our consideration and study in aiding in the development of a health program for the nation, an intent to which we are by knowledge, experience and conviction committed, its fundamental objectives being an expansion of public health, maternal and child welfare services, approved care to the aged and medically indigent, and an extension of hospital and diagnostic facilities.

CASE REPORTS

SO-CALLED CHOLANGEITIS LENTA: REPORT OF A CASE DYING WITH ULCERATIVE ENDOCARDITIS*

By O. H. PERRY PEPPER, M.D., F.A.C.P., *Philadelphia, Pennsylvania*

CHRONIC cholangitis is one of those subjects about which everyone knows the same facts—but no one knows very many. Opinions differ in the current textbooks: Osler states that chronic cholangitis may possibly occur as a sequel to an acute process but that it is usually secondary to common duct obstruction; Meakins relates it to a previous acute cholangitis; Rehfuess, to acute cholecystitis or common duct obstruction. Bloomfield does not discuss the chronic forms. Stengel and Kern in the Nelson System describe only catarrhal jaundice and suppurative cholangitis.

Rolleston and McNee,¹ Samuel Weiss² and other writers of authoritative monographs divide the condition which they term "chronic catarrhal cholangitis" into those cases with calculus and those without—the latter group again being subdivided into cholangitis of the extrahepatic ducts and of the intrahepatic ducts. This latter group is stated to arise from poisons or bacteria brought to the liver by the portal vein or the hepatic artery. As predisposing conditions portal cirrhosis, chronic venous engorgement, hepatitis and hepatic malignancy are mentioned.

From this sampling of the views of authoritative writers on this subject, it is easy to see the lack of definite knowledge. Some consider chronic cholangitis identical or a part of catarrhal jaundice, others derive it from acute suppurative cholangitis. In view of this confusion, it is not surprising that efforts have been made to describe certain sub-groups of cholangitis. Perhaps the most interesting of these types is so-called cholangitis lenta. This is interesting not only because of the concept involved, but also because of the extensive literature on cholangitis lenta in German and Italian. The only English references to this term which I have found occur in an article on gall-bladder disease by Held³ who reports a case due to *Streptococcus viridans* and in the Year Book for Medicine for 1934 in which Eusterman⁴ abstracted a German article by Harnisch.⁵

The term "cholangitis lenta" was chosen in 1921 by Schottmüller⁶ as might be expected to describe a special type of infectious cholangitis which was thought by him to present many analogies to endocarditis lenta. According to those who have written on this subject, this form of infection of the finer biliary passages develops as a primary condition, probably from ascending infection; it is not a suppurative process; it develops in the absence of gall stones and resembles endocarditis lenta. This resemblance rests on the insidious onset, the picture of slow sepsis with fever, anemia and splenomegaly and the prolonged course. Furthermore, the infecting bacterium is a streptococcus—often but not always the *Streptococcus viridans*—although some of the writers insist

* Received for publication May 27, 1938.

that the term cholangitis lenta can be used only if the streptococcus is of the viridans variety. Others feel that it is the course and clinical picture which justify the term rather than the exact type of bacterium.

There is nothing new in the fact that among the infecting agents causing cholangitis various types of streptococci are occasionally found. However, our literature has not stressed streptococcal cholangitis as an entity nor the form to which others have applied the term "lenta." Even if we do not approve of the term "cholangitis lenta," there may be something of value in the concept of a type of streptococcal cholangitis with many analogies to endocarditis lenta, although the prognosis may be better.

The individual articles in the literature on cholangitis lenta scarcely need to be reviewed at this time but one or two deserve mention. Eickhoff,⁷ in 1922, was an influential advocate of the new entity but based his arguments chiefly on the similarities of this type of cholangitis with endocarditis lenta, claiming that both were caused by the same *Streptococcus viridans*. Loewenhardt,⁸ however, in the next year applied the term to cases due to other bacterial forms, and Hedinger,⁹ in 1924, used the term for a case in which the infecting organism was the colon bacillus and stressed the possibility of a transition of the process into biliary cirrhosis. Umber¹⁰ reported a case in which the infection was with paratyphoid B. It was at about this time that Aschoff emphasized the frequency of biliary infections by intestinal bacteria and d'Antona¹¹ emphasized this source of the infection in cholangitis lenta. Rössle¹² in the section on inflammation of the liver in Henke and Lubarsch devotes half the space allotted to chronic cholangitis to the "lenta" form.

Not all of the writers on this subject are unanimous in accepting the syndrome; for example, Sotgiu,¹³ in 1933, felt that only a few of the reported cases deserved to be so diagnosed. However, the same year Harnisch⁵ attempted to describe a characteristic picture for the disease. Still more recently, La Manna¹⁴ has reviewed the evidence and comes to the conclusion that the diagnosis cholangitis lenta is justified only if the patient presents the picture of slow sepsis and if proof is obtained of the presence of chronic cholangitis. Rosenthal,¹⁵ in his monograph in 1934, mentions the use of the term in cases which resemble a chronic sepsis and agrees that other bacterial forms than the *Streptococcus viridans* may be responsible. In Eppinger's¹⁶ excellent book he states that although he has never seen such a case the diagnosis of cholangitis lenta should not be difficult because of the obvious septic syndrome with fever, endocarditis and nephritis. He does not amplify this final statement which is unfortunate in view of the case which aroused our interest in this subject.

CASE REPORT

The patient, a 36 year old janitor of good habits, entered the Medical Division of the University Hospital because of jaundice and weakness. At the age of seven he had suffered an attack of rheumatic fever with residual mitral damage. In recent years, he had some dyspnea on exertion and occasionally ankle edema and hemoptysis. A year before admission an episode of distinct cardiac decompensation occurred but was entirely relieved by digitalis which he continued until the appearance of the present illness, two months prior to admission. Jaundice, weakness and loss of weight increased rapidly and he came to us with a tentative diagnosis of carcinoma of the head of the pancreas.

In the Hospital the outstanding findings were intense jaundice, marked emaciation and mitral heart disease with auricular fibrillation but without failure of compensation. The abdomen seemed distended, there was some little tenderness and rigidity in the right upper quadrant, but no enlargement of the liver or spleen could be demonstrated. There was only a trifling anemia and no leukocytosis. Blood culture, serologic tests for syphilis and a variety of other laboratory investigations and

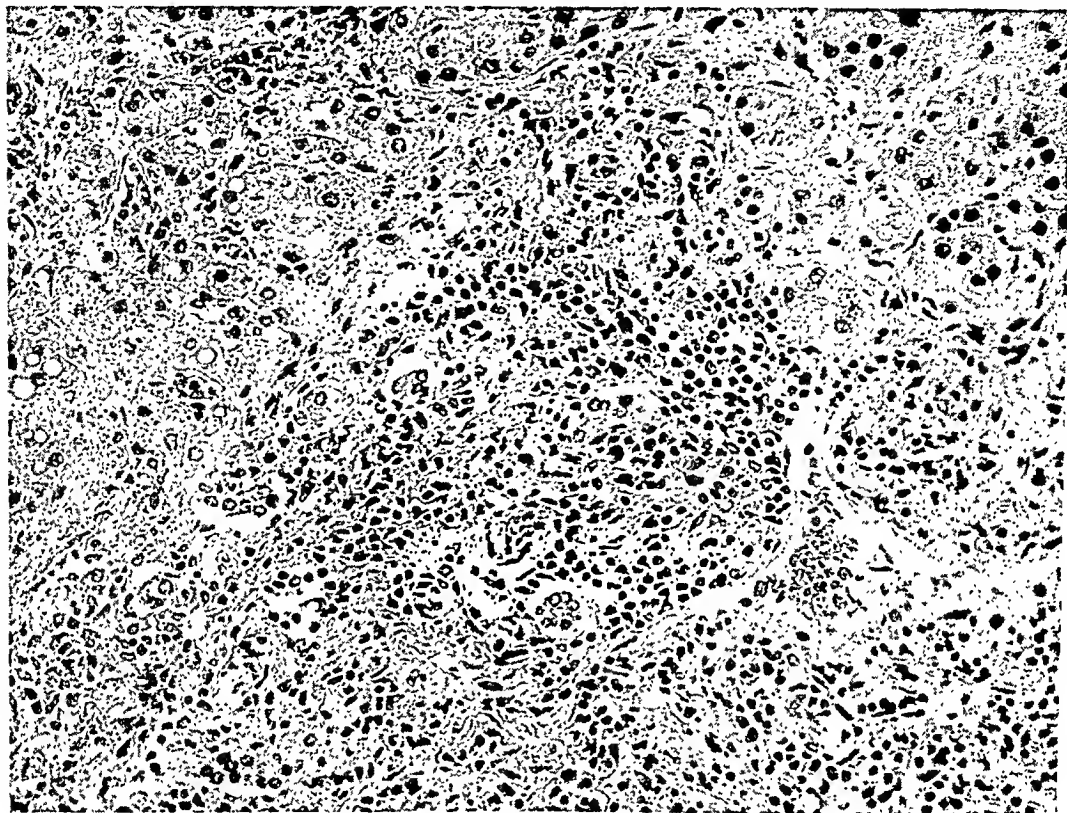


FIG. 1. Section of liver stained with hematoxylin-eosin (high power).

roentgen-rays which need not be detailed were negative. The van den Bergh test gave an immediate direct reaction with 14 units indirect. There was some bile in the stools; the biliary drainage showed nothing significant except for the presence of many pus cells. The patient did not appear seriously ill; there was a moderate irregular fever.

It was agreed that the circulatory state could not explain the jaundice; some felt that the diagnosis was long-standing catarrhal jaundice, others favored stone, still others malignancy. For a month conditions changed but little and surgical exploration was thought advisable. At operation, the gall bladder and common duct were found normal, no calculi were found; the liver, however, was distinctly abnormal, the surface being grayish and irregular. The operative diagnosis was cirrhosis of the liver.

Three weeks after operation, the patient was transferred back to the medical ward. There had been little or no fever for a week before transfer. However, soon after transfer January 11, 1937, fever returned and the second phase of this patient's illness developed. The fever was apparently not related to the surgical wound; the leukocyte count was not elevated. There was no distinct change in the cardiac or circulatory conditions, and various laboratory studies failed to shed any light on the

cause of the irregular fever which continued in the neighborhood of 102° F. After two weeks a few red cells began to appear in the urine, and after another two weeks the blood culture was positive for the first time and gave a growth of beta hemolytic streptococci. Still later, macrophages appeared in the blood. Death occurred two months after the development of this phase of the illness.

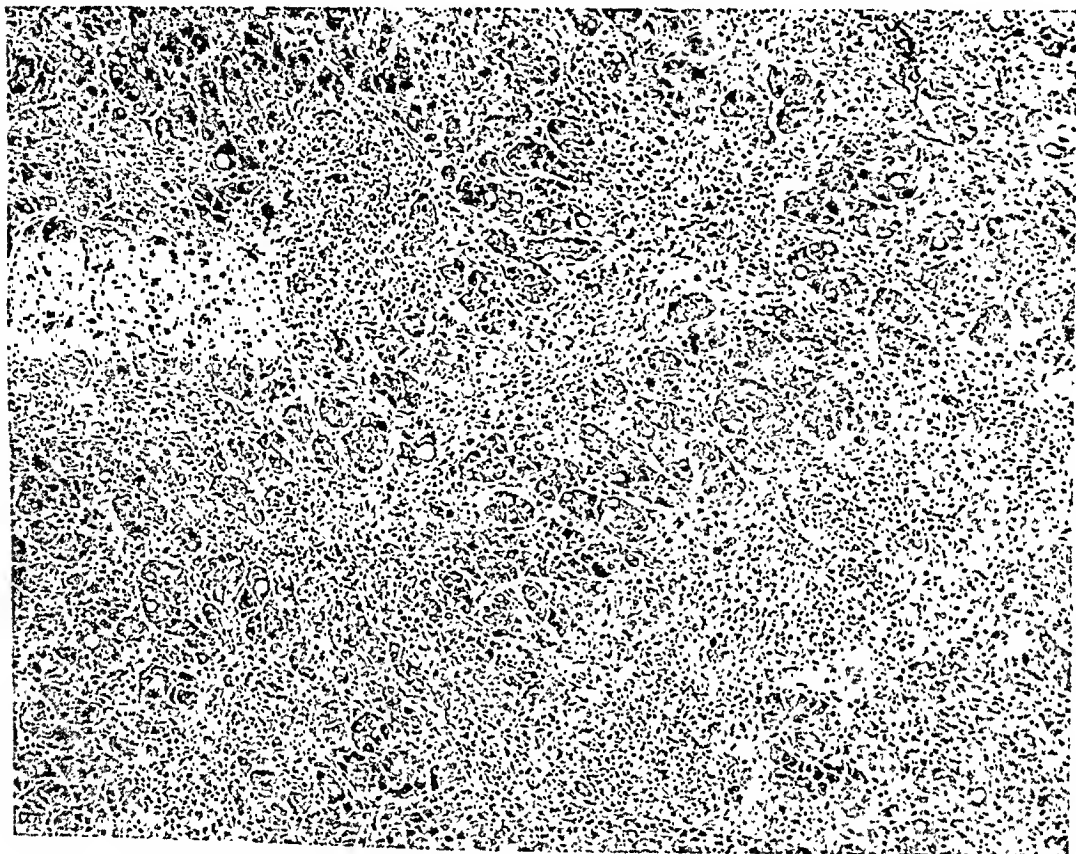


FIG. 2. Section of liver stained with Masson stain (low power).

Autopsy revealed, as was expected, an old rheumatic mitral heart disease, with moderate enlargement of the heart and some pericardial adhesions. Upon the chronically diseased anterolateral mitral leaflet there was a recent extensive ulcerating endocarditis. The spleen was moderately enlarged and two large yellow infarcts were present. The liver weighed 1360 grams but looked smaller than normal; it had a mottled granular surface. Nothing noteworthy was found in the gall-bladder or common duct. Microscopic examination by Professor Balduin Lucke led to the following report: The liver architecture is distorted with separation of the parenchyma into islands by loose strands of connective tissue, particularly around the interlobular biliary canals. In the meshes of this connective tissue are many lymphocytes and polymorphonuclear leukocytes. Some of the bile ducts are normal but others show inflammatory changes, still others have undergone proliferation. In certain areas entire lobules of liver parenchyma have been lost; elsewhere regeneration has replaced the degenerated tissue. The final picture is the result of degeneration, regeneration and overgrowth by inflammatory fibrous tissue and justifies the diagnosis cholangitis and pericholangitic cirrhosis. In the inflammatory foci in sections stained with Giemsa's solution there were found occasional paired cocci, probably streptococci.

DISCUSSION

This case obviously raises some interesting speculations for some of which, unfortunately, the answers are lacking. It would seem, perhaps, to be the type of case to which the diagnosis *cholangitis lenta* would be applied by those who use this term. Such cases are, however, not peculiarly rare, but in this patient there happened to exist an old valvulitis to which the streptococcic infection spread, thus establishing in this patient two conditions to which the term "*lenta*" might perhaps be applied although the endocarditis here was due to beta hemolytic streptococci. Possibly the chronic venous engorgement incident to the mitral heart disease predisposed this patient to a localization of infection in the liver which, in turn, acted as a focus from which the infection spread to the heart valve. This coincidence would seem to make this case unique unless Eppinger's inclusion of the word endocarditis among the septic manifestations of *cholangitis lenta* refers to such a picture, which seems doubtful.

As was said before, the term is not important but it would appear that the concept is and that it deserves more recognition in this country. It is probable that at present such cases are not being recognized and are being confused with catarrhal jaundice, suppurative *cholangitis* secondary to gall stones or duct obstruction, or with so-called biliary cirrhosis.

It would seem that the syndrome of primary streptococcal *cholangitis* should be accepted, that its "*lenta*" nature should be recognized. Its potentialities are several—it may act as a focus of infection, giving perhaps what was formerly termed biliary rheumatism—it may continue until the picture of biliary cirrhosis results—or it may act as a source of bacteremia with secondary localization if local conditions favor this—as occurred in this case in which previous rheumatic disease permitted the streptococcus to establish endocarditis as well as the original *cholangitis*—two conditions to which the term "*lenta*" has been applied.

REFERENCES

1. ROLLESTON, H., and McNEE, J. W.: Diseases of the liver, gall bladder and bile ducts, 3d ed., 1929, Macmillan and Company, New York.
2. WEISS, SAMUEL: Diseases of the liver, gall bladder, ducts and pancreas. Their diagnosis and treatment, 1935, Paul B. Hoeber, Inc., New York.
3. HELD, I. W.: Gall bladder disease with atypical symptoms, *Med. Clin. N. Am.*, 1935, xix, 649.
4. EUSTERMANN, GEORGE B.: Diseases of the digestive system and metabolism, Year Book Gen. Med., 1934.
5. HARNISCH, P.: Über Cholangitis lenta, *Deutsch. Arch. f. klin. Med.*, 1933, clxxvi, 81.
6. SCHOTTMÜLLER: Über Cholangitis, *Dem. Aerz. Ver. Mamburg, Münchn. med. Wchnschr.*, 1921, li, 1667.
7. EICKHOFF, F.: Ueber chronische Cholangitis (*Cholangitis lenta*), *Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, 1922, xxxv, 439.
8. LOEWENHARDT, F. E. R.: Zur Frage der Cholangitis lenta, *Klin. Wchnschr.*, 1923, ii, 192.
9. HEDINGER, E.: Cholangitis lenta, *Schweiz. med. Wchnschr.*, 1924, liv, 321.
10. UMBER, F.: Zur Diagnose und Behandlung der Krankheiten der tieferen Gallenwege. Klinischer Vortrage; *Deutsch. med. Wchnschr.*, 1929, lv, 2167.
11. D'ANTONA, L.: Epatocolangiti subacuta e lente, *Gior. d. med. prat.*, 1932, xiv, 443.
12. RÖSSLE, R.: In *Handbuch der spez. path. Anat. and Hist.*, 1930, v, 277, Henke and Lubarsch, Berlin.

13. SOTGIU, G.: Intorno alle cosi dette colangie e colangiti lente. Studio critico e contributo clinico, *Minerva med.*, 1933, i, 481.
14. LA MANNA: Über die sogenannte Cholangitis lenta, *Virchow's Arch. f. path. Anat.*, 1936, CCXCVIII, 515.
15. ROSENTHAL, F.: Diseases of the liver and biliary passages, 1934, Berlin.
16. EPPINGER, HANS: Die Leberkrankheiten, 1937, Springer, Wien.

HEREDITARY HEMORRHAGIC TELANGIECTASIS OCCURRING IN SIX GENERATIONS*

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HEREDITARY hemorrhagic telangiectasis, as found in more than six generations of an English family, is a rarity of interest. This condition may be sometimes overlooked because the general practitioner is not familiar with it as an entity.

Osler¹ described a series of three cases in 1901 and commented on an additional case reported by Rendu in 1896. Since then this condition has been called the Rendu-Osler disease. In 1907, Osler² wrote that telangiectatic areas in the skin increase as age advances, and that in the young such telangiectases are often temporary in character. He also noted that telangiectatic areas were associated with cirrhosis of the liver and with early internal malignant growths.

Hurst and Plummer,³ in 1932, reported that the literature at that time contained but 57 family trees in which there was indisputable proof of the disease.

Larrabee and Littman⁴ suggest that the following three postulates should be satisfied in order to establish the diagnosis:

1. A positive family history.
2. Telangiectatic areas typical in distribution, character and number.
3. A definite tendency for such spots to bleed.

In reviewing the first rule above, it must be said that either men or women may have the disease and that both sexes may transmit it to their offspring. Fitzhugh⁵ reported that one generation often is skipped only to have the disease appear insidiously in the next. He states that this occurred seven times in 212 cases. In some of such instances a very mild type of the disease may have been overlooked in the generation which was apparently "skipped."

The distribution, number and character of the telangiectatic areas are important. They may occur anywhere on the external surfaces of the body or on any of the various mucous membranes. On the skin they are more commonly found on the cheeks, nasal orifices, lips, ears, neck, scalp, fingers and trunk. The mucosa of the nasopharynx is seemingly most often affected, followed in frequency by the tongue, palate, inner cheek, pharynx, larynx, stomach, colon, bladder and brain. Lesions in the stomach, colon, bladder and brain are extremely rare.

Associated anomalies have been recorded. Fitzhugh⁶ has reported splenic and hepatic enlargement. Perhaps the increase in size of these organs may be

* Received for publication May 22, 1937.

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due to angiomas which have expanded within them. The case described below had an easily palpable mass projecting from the liver.

Given a clinical picture fulfilling the postulates as listed above, one can feel fairly certain of the diagnosis. One must bear in mind, however, that practically everyone has telangiectatic areas on some parts of the body which usually have escaped detection because they produce no symptoms.

The lesions are most often described as small red or purple spots, usually of pin point size, though sometimes larger, and even, in certain rare instances, of spider-like configuration. The lesions may or may not disappear on pressure. Sometimes they may come and go in crops without apparent reason.

Bleeding is variable. Sometimes there is profuse hemorrhage, which in some reported cases has caused death. Fitzhugh⁶ reports that in families known to have the disease, he found a mortality of 4 per cent from hemorrhage. Usually there is only a moderate bleeding tendency, which may cause secondary anemias and considerable incapacity from nasal and oral hemorrhage, difficult to check. Such bleeding occurring in the rectum, bladder, larynx and stomach, may account for some of the so-called "idiopathic hemorrhages" that have been described in the past. Trauma is not necessary, for bleeding occurs spontaneously without injury or irritation. Some cases have nasal hemorrhage three or four times daily for weeks at a time. It is Steiner's⁷ opinion that bleeding occurs first and that the telangiectatic areas appear only after the initial hemorrhage.

One should be cautious in diagnosing the disease in childhood. Usually the bleeding is not noted until the age of 12 or 14 and if one examines younger children of families whose parents have the disease, they may or may not show telangiectatic areas. On the other hand Weber⁸ has reported a case of telangiectasia, not hereditary in origin, which first began to appear on the skin and mucous membranes at 67 years of age. Hereditary cases have histories of having no "spots" on their face until 12 or 16 years of age and having them then appear gradually and later start bleeding. Meikle⁹ has stated that the maximum development of these lesions tends to occur in the fourth decade.

The differential diagnosis of hereditary hemorrhagic telangiectasis is not a difficult problem. The disease is unlike hemophilia in that it appears in women, is transmitted by both sexes and not by women only, and is not characterized by delayed coagulation time. Thrombocytopenic purpura should not be confused with telangiectasia because in the former one finds a greatly reduced platelet count, delayed bleeding time, normal clotting time, absence of clot retraction and a positive capillary fragility test. It is well to emphasize that all blood studies are normal in hereditary hemorrhagic telangiectasia unless there is secondary anemia from blood loss.

Meikle⁹ considers subacute bacterial endocarditis in differential diagnosis because in both conditions one may have to deal with an ill patient with a café au lait complexion, pyrexia, a variable number of hemorrhagic spots on the lips, conjunctivae and fingers, and splenomegaly. The history of the development of the telangiectases, the characteristic morphology of these lesions, as well as the normal cardiac findings and lack of blood stream infection should clearly differentiate these conditions.

Studies on the histopathology of the disease have been conducted by Hanes¹⁰ and by Steiner.⁷ The dilated walls of the affected vessels are composed of but one layer of endothelium and are covered by an extremely thin layer of epi-

dermis or mucosa. There is no elastic layer in such dilated vessels, and hence once a hemorrhage does commence there is little power of the walls to contract.

Numerous therapeutic measures have been instituted; observers vary as to their efficacy. Houser,¹¹ of Philadelphia, on the basis of a large experience concludes that the chromic acid bead is the most effective local therapy. He finds



FIG. 1. Telangiectases on tongue and upper lip.

that new areas may appear on essentially normal mucosa after cauterization has been used. His results were not as good with radium, roentgen-ray, electrocoagulation or galvanocautery as with chromic acid bead treatment. He advocates general measures such as high vitamin diet, iron, liver, and rest when needed. Fitzhugh⁶ has found that patients with hereditary hemorrhagic telangiectasis, who have Moss type IV blood, are intolerant to transfusion, and this

is more marked in patients with hepatomegaly and splenomegaly. Two cases out of a series of four with the above findings died of severe transfusion reactions associated with post-transfusion jaundice.

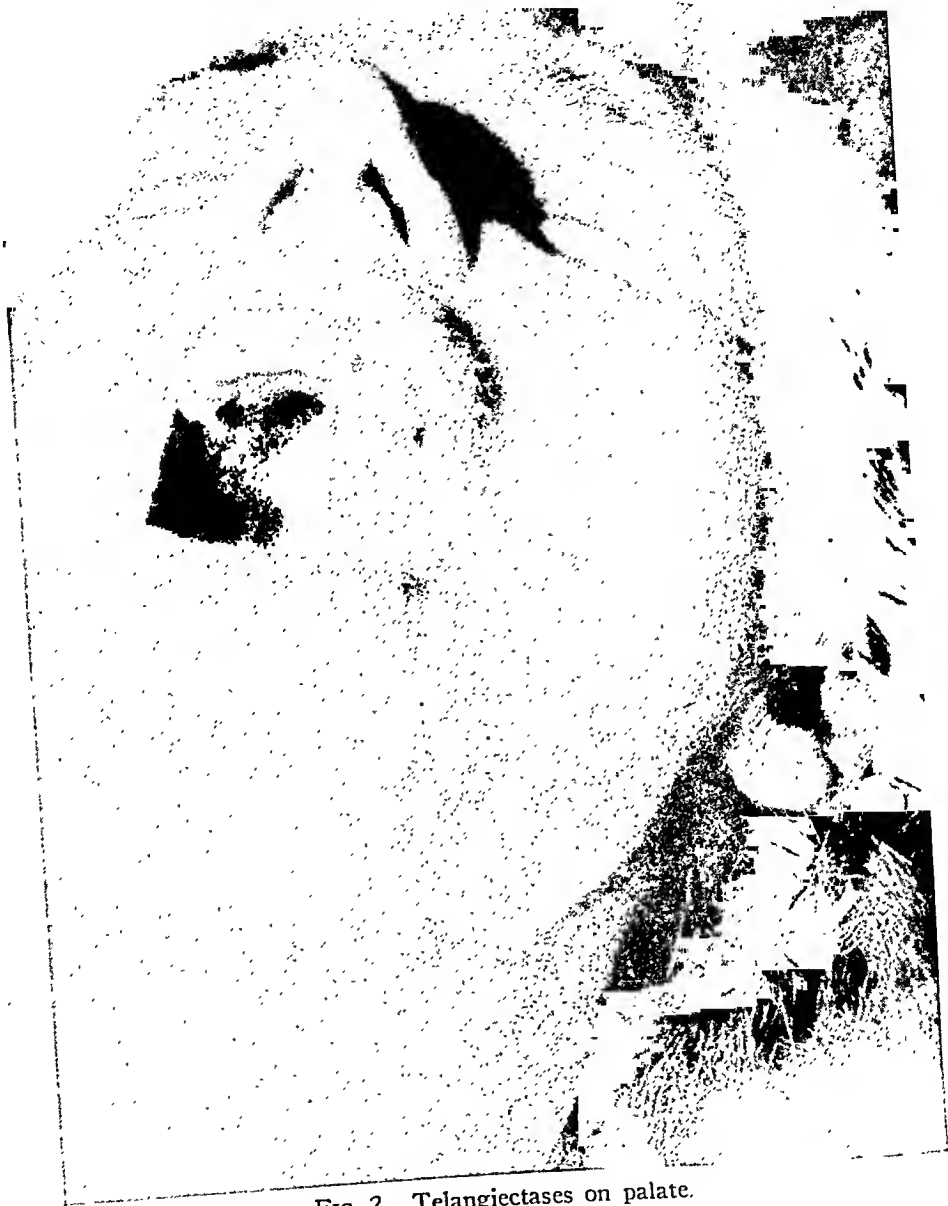


FIG. 2. Telangiectases on palate.

Cases with a genuine family history are prone to have about a 4 per cent mortality due to uncontrolled epistaxis. If sufficiently severe, bleeding will cause secondary anemias with resultant decreased resistance, which in turn may precipitate various infections. The disease may be said to be more severe in the ages between 40 and 50 and thereafter a decrease in bleeding is to be expected.

CASE REPORT

Mrs. Emma H., aged 45, entered the Rhode Island Hospital on September 21, 1936 with three chief complaints, nose bleeds, psoriasis and arthritis. She had had

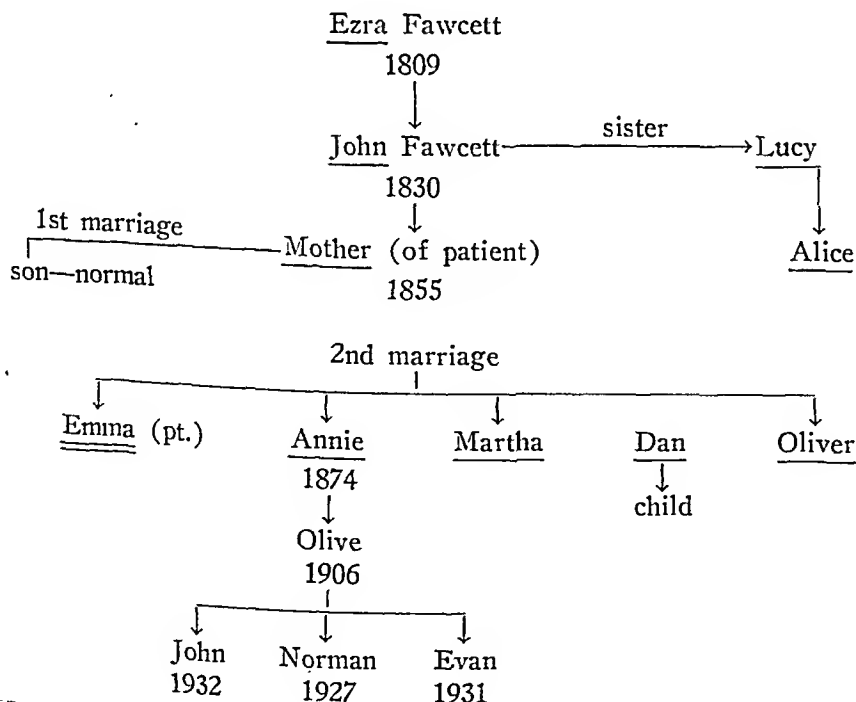
epistaxis ever since she was 16 years old and the bleeding had gradually increased in severity with her age. On admission each hemorrhage might last as long as two days and continue constantly during the day and night. The patient also bled from the mouth on rare occasions. The nasal bleeding tended to recur every few days and often an interval of two weeks might intervene. The slightest trauma or coryza would precipitate attacks. Bleeding also might come without any precipitating symptoms or signs. Lately after spells of bleeding the patient complained of marked dyspnea and weakness and some slight ankle edema. The patient treated her hemorrhages with cotton immersed in hydrogen peroxide; this gave poor results.

The psoriasis was of 19 years' duration, and had decreased in severity. The lesions were on the extensor surfaces of her arms, knees, ankles, thighs and also on her back. None of the many past dermatological treatments benefited the patient.

Eight years ago arthritis affected her left hip; soon it progressed to the right hip, knees, feet and finally her hands and fingers were involved. Her knees had been from time to time red and warm and her ankles on occasion had been black. The arthritis was aggravated by damp weather. About a year and a half ago, the patient seemed cured of all joint involvements and at that time she had no limitation of movement. There was on admission some swelling and stiffness in her knees and a rather numb feeling was usually present.

Past History: The patient stated she had been weak all her life. Historical review of the head, eyes, ears, sinuses, mouth, teeth, throat, larynx, nose, urinary, cardiac and respiratory systems was negative except for the present illness. The patient had anorexia for years and lately vomited after nosebleeds. No blood was noticed in the vomitus. Otherwise, the gastrointestinal system was negative. Her menses began at 13 and her menstrual flow was usually scanty, without pain or intermenstrual discharge. She denies any venereal disease. There were no neurological symptoms. She had never been pregnant.

Family History: The family tree outlined here will serve to simplify this part of the history.



The informant was Annie, sister of the patient. Annie very dramatically told how her mother, in bygone days, tried to reconcile her children to their fate and impressed upon them that their affliction was known, in their family history, as the *Fawcett Marks*. Some folk in the countryside believed that the Fawcett family were disfigured because one of their ancestors committed a grave sin.



FIG. 3. Retrograde pyelogram showing tumor in right kidney.

This family are natives of Yorkshire, England. Many of their relatives still live there. In the *first* and *second generation* Ezra and John Fawcett are known to have spots on their faces. John's sister Lucy had her face rather severely disfigured by red spots. In the *third generation* her daughter Alice's cheeks were markedly disfigured. John's daughter who was the patient's mother "bled wickedly" for over 40 years. She subsequently died of "cancer of the liver." Sometimes she bled two or three times a day. It was not uncommon for her to bleed daily for weeks at a time from her cheeks and lips. She was married twice. In the *fourth generation* her first marriage resulted in one child who was perfectly normal. Her second marriage, however, resulted in seven children, five of whom were afflicted with this disease. Emma, our patient, has been discussed. Annie has been handicapped because of her telangiectasia. Her lesions are located in back of her ears, on both cheeks, in both nasal folds, on the neck, several large red spots on the tongue, two on her finger tips and a few on her scalp. When she was younger she had numerous spontaneous hemorrhages

from the scalp and face, and on one occasion there was a pulsating hemorrhage from the right nasal fold. These would occur spontaneously whether at rest or work. Martha bled from the lip and tongue, when younger. The many spots on Dan's nose and cheek frequently hemorrhaged. Oliver died "probably from lack of blood" when he was 20 years of age and he "bled terribly like his mother." In the *fifth generation*



FIG. 4. Psoriasis on legs.

Olive had many nose bleeds after she was 14 and only recently had she failed to be troubled. She had no visible telangiectatic spots when examined. In the *sixth generation* Norman, her oldest boy, bled easily and abnormally from the nose and had one red spot in the nasal fold, none elsewhere. John and Evan had no bleeding, but both had a telangiectatic red spot on the mucosa opposite the last molar tooth and Evan had a spot on the right cheek.

Physical Examination: The patient was a weak, slightly emaciated woman. She

had prominent eyes and café au lait color of her skin. There was no cyanosis, jaundice or orbital edema. On her face were a few diffuse blemishes. The right pupil was slightly irregular, the left was round. Both reacted to light and on accommodation. The extra-ocular muscles were normal as were the fundi. The nasal mucosa was a bright reddish-pink color. There were numerous, injected, bright red areas in the right and left nasal fossa about two mm. in diameter. The turbinates were not swollen. One in the left nasal fossa was stellate. On the edge and in the center of the tongue there were red spots, pin-head size, and not especially raised above the surface. The roof of the mouth had three similar areas, but larger, two to three mm. in diameter. The tonsils were large and cryptic. The lungs were entirely negative except for a few fine crackling râles at both bases. Pulse was 125, blood pressure 140 systolic and 88 diastolic. There was no cardiac enlargement, no precordial thrills or heave. A soft, blowing, systolic murmur was heard over the apex transmitted to the aortic area. The abdomen was full, round and soft. The kidneys and spleen were not palpable. A hard, tongue-shaped mass, about 5 cm. wide and 9 cm. long, was felt in the right upper quadrant and seemed to be connected with the liver. This mass was a bit to the right of the mid-line and descended with respiration. Rectal and vaginal examinations were negative.

The skin had psoriatic lesions over all the extensors: white scales which chipped, and these were on top of hard, dry, raised, cracked areas. There was slight to moderate swelling of all the joints and some limitation of movement in the knees and hands with corresponding decrease in strength. The reflexes were normal. There was no general glandular enlargement.

Laboratory: The hemoglobin was 60 per cent. The red blood cell count was 3.7 million, and the red blood cells were pale. The white blood cell count was 5.2 thousand, and the platelets 210 thousand. The differential count was polymorphonuclears 85 per cent, eosinophiles 1 per cent, lymphocytes 13 per cent, monocytes 1 per cent. The mean corpuscular volume was 100.7. The Wassermann was negative. The blood urea nitrogen was 16 mg., sugar .91 mg., calcium 9 mg. and the sedimentation rate was 10 minutes. The fragility was .36-.30. Coagulation time 1 minute 20 seconds, bleeding time 1 minute 15 seconds. The patient's blood was classified as Group II (Moss).

Stools were positive for occult blood. The urine was essentially negative. Fluid from the right knee was withdrawn and numerous pus cells but no organisms were seen on smear. Cultures demonstrated fine slender unidentified gram negative rods. Guinea pig inoculation was negative. Two subsequent taps were negative to cultural growths. The electrocardiogram was not remarkable.

On October 19, 1936, the roentgen-ray examination of the chest showed clear lung fields. The heart and great vessels were not enlarged.

On September 25, 1936, the roentgen-ray department reported an area of increased opacity on the right side of the abdomen extending from the inferior surface of the first lumbar vertebra down to the iliac crest which might be due to an enlarged kidney or tumor. There was a group of irregular dense shadows above the right sacro-iliac region and these were attributed to calcified glands.

On November 13, 1936, a retrograde kidney examination was done. The bladder urine had very few pus cells, no organisms were seen, no tubercle bacilli were found and there was a sterile culture. The kidney urine revealed a few red blood cells on both sides, also sterile cultures and no organisms or tubercle bacilli were seen by smear. Phenolsulphonephthalein gave a three minute appearance time with 60 per cent concentration on the right side in 30 minutes, a four minute appearance time and 20 per cent reading on the left. Pyelograms showed some displacement of the dye with a large area of increased radiability in the pelvis of the right kidney which was ascribed to tumor. There was dilatation and blunting of the calices. The left kidney pelvis and calices showed no lesion. There was increased density of the bone in the region of both sacro-iliac articulations.

On November 24, 1936, the urology department concluded that there was a growth in the right kidney and that function of the left kidney was very poor. It was the consensus of opinion that operation was inadvisable and that deep roentgen-ray therapy on the right side would be in order.

Treatment: The telangiectatic areas were treated with numerous applications of chromic acid beads and much improvement was noted and bleeding decreased markedly. "Feosol," an iron preparation, and liver extract were given for the anemia. Hemoglobin and red blood cells increased from findings on admission to 96 per cent and 4.7 million on discharge. The white count never varied from around 5.6 thousand. The sedimentation rate lengthened to two hours and nine minutes. The urine was always negative. With the exception of an elevated temperature (101°) and increased pulse rate during the first 10 days, the clinical chart was normal.

The dermatologists treated the psoriasis with "sulisocol" intravenously in the hope it would benefit the arthritis. Diathermy and gentle massage were advised by the orthopedists and were of value.

Result: The patient was discharged on November 24, 1936. There was marked improvement in her general health and appearance. There was only an occasional spotting of blood from the nose. The psoriasis was slightly improved and the arthritic manifestations were greatly benefited.

SUMMARY

Hereditary hemorrhagic telangiectasia is briefly traced through six generations. Literature, differential diagnosis, and treatments are discussed. One case is reported in detail.

BIBLIOGRAPHY

1. OSLER, W.: A family form of recurring epistaxis associated with multiple telangiectasis of the skin and mucous membranes, *Johns Hopkins Hospital Bull.*, 1901, xii, 333.
2. OSLER, W.: On telangiectasis circumscripta universalis, *Johns Hopkins Hospital Bull.*, 1907, xviii, 401.
3. HURST, A. F., and PLUMMER, N. S.: Hereditary hemorrhagic telangiectasis with hemorrhagic tendencies, *Guy's Hospital Rep.*, 1932, lxxxii, 81.
4. LARRABEE, R. C., and LITTMAN, D.: Hereditary hemorrhagic telangiectasis, *New England Jr. Med.*, 1932, ccvii, 1177.
5. FITZHUGH, T.: The importance of atavism in the diagnosis of hereditary hemorrhagic telangiectasis, *Am. Jr. Med. Sci.*, 1923, clxvi, 884.
6. FITZHUGH, T.: Splenomegaly and hepatic enlargement in hereditary hemorrhagic telangiectasia, *Am. Jr. Med. Sci.*, 1931, clxxxi, 261.
7. STEINER, W. S.: Hereditary hemorrhagic telangiectasia, *Arch. Int. Med.*, 1917, xix, 194.
8. WEBER, F. P.: Hemorrhagic hereditary telangiectasia of Osler type, *British Jr. Dermat. and Syphil.*, 1936, xlviii, 182.
9. MEIKLE, G. J.: Hemorrhagic hereditary telangiectasia, a case, *Lancet*, 1933, ii, 863.
10. HANES, F. M.: Hereditary hemorrhagic telangiectasis, *Johns Hopkins Hospital Bull.*, 1909, xx, 62.
11. HOUSER, K. M.: Hereditary hemorrhagic telangiectasis, *Ann. Otol., Rhinol. and Laryngol.*, 1934, xliii, 731.

TREATMENT OF PNEUMOCOCCIC MENINGITIS (TYPE XV)
WITH PARA-AMINO-BENZENE-SULFONAMIDE

(REPORT OF A CASE WITH RECOVERY) *

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THIS case report attempts to present further^{15, 16} evidence concerning the efficacy of sulfanilamide in pneumococcic meningitis. That sulfanilamide and its derivatives are of definite value in the treatment of streptococcic^{1, 2, 3, 4, 5, 6} and meningococcic meningitis⁷ has been proved by thorough experimental work and frequent clinical findings. The value of sulfanilamide in the treatment of various types of pneumococcic infections is as yet undetermined. However, recent reports in the literature suggest that this drug may be of value in the treatment of type III pneumococcic infections,^{8, 9, 10, 11, 12, 13, 14} and is more definitely of value in certain types of pneumococcic meningitis.^{15, 16, 21} Its relative value in comparison with sulfapyridine is in process of determination in many clinics.

Available statistics bear witness to the fact that pneumococcic meningitis has heretofore been associated with a very high rate of mortality.^{15, 16, 17, 18, 19}

CASE REPORT

E. T., a 22 year old white male, an engineer by profession, was admitted to Mercy Hospital on March 1, 1938 to the private rhinological service of Dr. Waitman F. Zinn. He complained of pain and swelling of the right side of the face, extreme headache, and malaise.

Past History: He had been suffering with recurring head colds and headaches for the entire winter, and on February 24, 1938 (the first day of his illness), he developed an acute right maxillary sinusitis which manifested itself by pain and swelling of the entire right side of the face and extreme headaches. He was seen by his family physician who referred him on February 28 to Dr. W. F. Zinn. At this time the patient was quite ill. Local swelling had increased to such an extent that the right eye had swollen shut. A trocar puncture was done through the right nasal cavity which produced much thick purulent material. Unfortunately, a culture of this purulent material was not taken at this time. The next day irrigation of this antrum was attempted, but was unsuccessful because of the increased viscosity of the material. The patient's general condition seemed much worse and hospitalization was advised.

Physical Examination: This patient presented himself as a well developed, well nourished, young adult male who complained of pain and swelling of the face and extreme headache. He moaned continuously and seemed very toxic. He was very disinclined to answer questions; however, when sufficiently urged he answered intelligently. The entire right side of the face was swollen causing his right eye to be tightly closed. There was marked local elevation of temperature and extreme tenderness of the entire right side of face. The pupil of the left eye reacted to light and accommodation. Extra ocular movements were normal but caused some complaint of pain on the part of the patient. Examination of the ears was negative. The mucous membrane of the nose was swollen so as to entirely occlude the breathing spaces. There was only a small amount of tenacious discharge from the right nasal cavity. A smear taken at this time of this material revealed streptococci, staphylococci, and various other organisms. The mouth was rather dry and sordes were

* Received for publication April 29, 1938.

present on the teeth. The pharynx was injected, and showed some evidence of post-nasal drip. There were a few slightly enlarged tender lymph nodes on both sides of the neck. Transillumination of the sinuses revealed marked clouding of the right maxillary antrum. There was no suggestion of cervical rigidity. Chest expansion was ample and equal on both sides. Percussion note over the lung fields was resonant throughout and the breath sounds were normal. The respirations were regular, rather deep and were 17 per minute. The heart outline was within normal limits. The heart sounds were angry and the rate was 100 per minute. The radial arteries seemed very leathery, the pulse was bounding but regular. The blood pressure was 110 systolic and 70 diastolic. The abdomen was entirely negative. The extremities were negative. Deep and superficial reflexes were entirely normal. There were no pathological reflexes. There were no petechiae or skin rash. Oral temperature was 99.4° F.

Admission Laboratory Findings: The blood picture revealed hemoglobin 17.8 grams or 104 per cent; red blood cells 4,850,000; white blood cells 10,000. The differential count showed 67 per cent segmentocytes, 10 per cent staff forms, 11 per cent lymphocytes, and 12 per cent monocytes. The admission urine specimen showed albumin 3 plus, 10 leukocytes per high power field and 1 erythrocyte. A blood culture was taken at this time which subsequently proved to be negative. Sedimentation rate (Wintrobe) registered 30 mm. per/60 minutes revealing marked acceleration. Blood sugar was 114; urea 35; and urea-N 17 mg. per cent.

Clinical Course: On the afternoon of admission the patient began to complain of recurring attacks of chilliness and his temperature rose to 101° F.

Therapy was instituted consisting essentially of forcing fluids, sedation, and sulfanilamide grains 10, four doses daily. Details of subsequent sulfanilamide dosage and blood and spinal fluid concentrations will be found in table 1. The next day, March 2, the patient's condition was unchanged except for increased toxicity and increasingly severe headache which caused him to moan continuously. His maximum temperature was 101.8° F. at 4 a.m. Irrigation of the right antrum was attempted and a small quantity of purulent material was washed out. It was quite evident that the sinus was not draining favorably. Another blood culture was done which also proved to be negative subsequently. Throughout the entire night and early hours of the morning of March 3, the patient tossed restlessly, and it was necessary to give pantopon frequently in order to produce even slight sedation. Early that morning he complained of pain in the posterior cervical region and increasing headache. He described this headache as a tight band of pressure which encircled the horizontal circumference of the head. By mid-day he was semistuporous. He complained bitterly of photophobia, and divergent strabismus was noticeable. His neck was retracted and examination revealed definite cervical rigidity. Kernig's sign was positive bilaterally. Babinski's sign was positive bilaterally, and Brudzinski's sign was negative. The deep reflexes were very hyperactive and equal. The respirations were of the Cheyne-Stokes type, and the pulse showed a slight irregularity (pulse 64 per minute during apnea and 80 per minute in the dyspneic phase). The eye grounds revealed slight papilledema. The maximum temperature was 103.4° F. He vomited six to ten times during this day.

Because of these findings a lumbar puncture was done which revealed very cloudy fluid with some fibrinous threads. The pressure was 340 mm. water. The cell count was 5,560 per cu. mm., predominately polymorphonuclears (78 per cent). A direct smear of this fluid (centrifuged) revealed no organisms but culture for 12 hours produced definite growth on blood agar. This was found to be a gram positive diplococcus which upon subsequent examination proved to be a pneumococcus. Repeated typing revealed this organism to be type XV pneumococcus.* Retyping was

* Identified by culture upon blood agar, solubility in bile and by Neufeld's quellung reaction using Lederle's rabbit serum.

done 10 to 15 times on subsequent spinal punctures and all results corroborated the initial finding that the organism involved was the pneumococcus type XV. The patient's headache was somewhat relieved by this initial lumbar puncture.

In view of these findings the sulfanilamide was increased to grains 60 per 24 hours and 250 c.c. of 25 per cent glucose were given intravenously twice daily. Lumbar punctures were performed two to three times daily. Details of the spinal fluid findings are recorded in table 1.

TABLE I

Date	Sulfanilamide Dosage/24 hrs.	Concentration		Pressure	Spinal Fluid Cell Count	Culture	Max. Temp.	Remarks
		Blood	C. S. Fluid					
3/1	40 grains	—	—	—	—	—	—	
3/2	40 grains	—	—	—	—	—	—	
3/3	40 grains	—	—	340 mm.	5,560	pos. pneumo. XV	103.4° F.	Blood cult. neg.
3/4	60 grains	2.5 mg. %	2.5 mg. %	140 mm.	4,200	pos.	101.4° F.	Blood cult. neg.
3/5	120 grains	6.2	4.0	140 mm.	4,050	pos.	100.2° F.	
3/6	120 grains	10.0	7.0	200 mm.	1,800	pos.		
3/7	120 grains	13.1	9.6	190 mm.	1,000	pos.	103° F.	Radical antrum
3/8	120 grains	12.9	10.0	200 mm.	550	pos.		
3/9	120 grains	11.4	7.1	240 mm.	2,220	pos.	101.2° F.	
3/10	120 grains	10.7	5.0	230 mm.	2,000	pos.		
3/11	120 grains	14.3	—	270 mm.	1,400	pos.		
3/12	120 grains	—	—	250 mm.	350	pos.	101° F.	
3/13	80 grains	—	—	210 mm.	400	pos.		
3/14	60 grains	6.2	4.4	190 mm.	320	pos.	103.4° F.	
3/15	35 grains	5.0	—	300 mm.	2,492	pos.		
3/16	discontinued	3.1	—	180 mm.	1,160	pos.		
3/17	—	—	—	150 mm.	801	NEGATIVE	101° F.	
3/18	—	—	—	190 mm.	1,120	NEGATIVE		
3/19—4/2	—	—	—	150 mm.	320	pos.	101° F.	
4/2/38	DISCHARGED	—	—	120 mm.	115	pos.		
		—	—	150 mm.	43	NEGATIVE	101.2° F.	
		—	—	No TAP	—	—	100.4° F.	
		—	—	No TAP	—	—	100° F.	
		—	—	No TAP	—	—	100° F.	
		—	—	No TAP	—	—	100° F.	
		—	—	No TAP	—	—	100° F.	
		—	—	No TAP	—	—	100° F.	
		—	—	95 mm.	11	NEGATIVE	99.6° F.	
		—	—	No TAPS	—	—		

All sulfanilamide given per os. One grain sodium bicarbonate given for every grain of sulfanilamide.

On each occasion of positive culture pneumococcus type XV recovered.

Queckenstedt normal on every occasion.

All temperatures on this chart are rectal temperatures.

March 4. The patient's general condition seemed slightly better. He rested at times during the night. His headache which had been eased by the initial lumbar puncture returned to a certain degree. The daily maximum temperature dropped to 101.4° F. The spinal fluid cell count dropped during this day from 4,050 cells per cu. mm. to 1800 cells per cu. mm. Respiration and pulse were regular during some periods of the day. March 5. The patient rested rather quietly during the early hours of the morning and continued clinical improvement was noticeable. Pulse and respiration were regular during the greater part of the day. He ceased moaning and his headache was slightly eased. The cervical rigidity decreased. Kernig's sign could not be elicited as easily as on previous examination. The daily maximum temperature dropped to 100.2° F. Spinal fluid cell count dropped from 1,000 to 550 during this day although the pressure remained about 200. The differential spinal fluid cell count revealed 70 per cent polymorphonuclears. Complete blood count was as follows: Hemoglobin 89 per cent or 15.2 grams; erythrocytes 4,500,000; leukocytes 16,900 per cu. mm. The differential white blood cell count showed 71 per cent segmentocytes, 7 per cent staff forms, 15 per cent lymphocytes, 5 per cent monocytes, 1 per cent eosinophiles. A blood culture was taken which subsequently proved to be negative.

On this day, the blood sulfanilamide concentration being only 6.2 mg. per cent in the blood, the fluids were restricted to 2,500 c.c. per day in an effort to increase concentration by decreasing volume of urinary output. The sulfanilamide dosage was increased to 120 grains a day. An indirect blood transfusion of 300 c.c. was given.

March 6. On this day his general clinical condition was slightly worse. He began to moan again at intervals and complained of pain in his legs. His headache had returned to a severe degree. Marked photophobia was present. At times slight disorientation was noticeable. His daily maximum temperature rose to 103° F. His spinal fluid cell count rose to 2,200 cells per cu. mm. and the pressure increased to 240 mm. of water. Roentgen-ray of the sinuses revealed marked cloudiness of the right maxillary sinus.

In view of these findings and the continued positive cultures of the spinal fluid, it was considered advisable to drain the right antrum by a radical approach. Dr. Waitman F. Zinn performed the operation using a basal avertin anesthesia and local nerve blocks. No free purulent material was obtained but the sinus was lined with a very thick coagulated mucopurulent exudate which was removed. The sinus was then packed with iodoform gauze. Culture from this sinus produced a *Staphylococcus aureus* and a few chains of diplococci which could not be separated and grown as a pure culture. The patient tolerated the operation well and was returned to his room in good condition.

March 7. The patient rested quietly almost the entire day and his general condition seemed much better. His cervical rigidity had decreased to a minimum and Kernig's sign was negative. He seemed slightly brighter and his irritability was markedly decreased. His maximum temperature was 101.2° F. Spinal fluid cell count was 350 per cu. mm. Spinal fluid pressure was 250 mm. water. Sulfanilamide concentration rose to 13.1 mg. per cent in the blood and 9.6 mg. per cent in the cerebrospinal fluid. The patient showed marked cyanosis which was attributed to the sulfanilamide. A complete blood count was as follows: Hemoglobin 80 per cent; erythrocytes 4,650,000; leukocytes 12,050. A differential white blood cell count revealed 60 per cent segmentocytes, 16 per cent staff forms, 7 per cent lymphocytes, and 8 per cent monocytes. A second blood transfusion of 300 c.c. was given.

March 8. The patient was more restless than on previous day and complained again of the severe headache. His temperature rose to 103.4° F. No other clinical change was noticeable. The spinal fluid cell count increased again to 2,492 cells and the spinal fluid pressure rose to 300 mm. of water.

March 9. The patient seemed very much improved. He rested quietly throughout most of the day and when awake seemed very bright. His headache was considerably eased. The maximum daily temperature was 101° F. The spinal fluid cell count was 801 cells and pressure was 150 mm. water.

The spinal taps done on this day produced the first negative cultures thus far.

March 10. Clinical improvement continued. Mental attitude improved, and the patient began to take a small amount of nourishment by mouth. Maximum temperature was 101° F. Maximum cerebrospinal fluid cell count was 320 cells per cu. mm., and maximum cerebrospinal fluid pressure was 150 mm. of water. The two spinal taps done on this day produced positive cultures but from this time on subsequent spinal taps were entirely negative.

March 11. The patient was very cheerful and alert. He welcomed conversation. He began to take nourishment in more ample quantity. He spent a very comfortable day. Cerebrospinal fluid cell count and pressure continued to drop.

March 12. Continued clinical and laboratory improvement.

March 18. The patient's clinical appearance continued to progress steadily towards recovery. Maximum temperature 99.6° F. Cerebrospinal fluid cell count

revealed 11 cells, all of which were lymphocytes. The cerebrospinal fluid pressure was 95 mm. of water. The culture was negative. This was the last spinal tap done and marked the sixth day of consecutive negative spinal fluid cultures.

March 30. Patient up per routine.

April 2. Patient discharged. No residua of meningeal signs or right maxillary sinus infection evident.

We consider it of importance to note that following the operation which consisted of a right radical antrum, the patient showed a marked improvement in clinical and laboratory findings. There was one return of rise in temperature and spinal fluid cell count which, however, was not accompanied by any marked return of untoward clinical symptomatology; temperature-pulse chart and laboratory findings progressed gradually but steadily towards normal. On March 8 the eighteenth day after admission, the patient's condition had progressed to the point where there were no clinical signs of meningitis and no subjective complaints. The patient left the hospital walking on April 2.

COMMENTS

Josephine Neal et al.¹⁷ in 1934 presented an analysis of 623 cases of meningitis other than meningococcic and tuberculous varieties. Two hundred and fourteen or 34 per cent of these cases were of the pneumococcic variety. In this series of 623 cases of various types of meningitis, 16 cases recovered. It is of importance to note that although they state specifically those varieties which recovered, the pneumococcic variety is not included in this list. In 1935 Josephine Neal¹⁸ reported 24 recoveries from meningitis (other than meningococcic) seen by her staff within the preceding 25 years. Pneumococcic meningitis was not among those varieties treated successfully. The same author¹⁵ in a more recently written article (1938) intimates that she has experienced 100 per cent mortality in pneumococcic meningitis prior to the adoption of sulfanilamide as a therapeutic agent in this disease. In the article just mentioned, the authors reported 14 cases of pneumococcic meningitis. Types of pneumococcus listed were I, III, IV, V, VI, VII, XIII, XIX, and XXXI. All 14 cases received sulfanilamide therapy. When specific serum was available it was given in addition to the sulfanilamide. Of the 14 cases, three recovered. The bacteriological types of pneumococcic meningitis to recover were types IV, XIX, and XXXI. None of these cases received serum. The three cases which recovered followed operative procedure on sinus or on otitic infections. This limited series of cases resulted in 21 per cent cures and 79 per cent fatalities. It is of significance to note that their previous figures concerning pneumococcic meningitis resulted in no cures and 100 per cent fatalities.^{17,18} Basman¹⁶ reported three cases of pneumococcic meningitis treated with sulfanilamide. One of these cases (Type V) recovered. This is the first recorded case of recovery at St. Louis Children's Hospital.

The case which we are reporting is one of type XV pneumococcic meningitis. We have been unable to find record of any other case of type XV pneumococcic meningitis. We have been unable to find any literature concerning the effect of sulfanilamide on type XV pneumococcic infections.

It is necessary to note that in our case a culture of the purulent material removed at operation from the right maxillary sinus revealed a great pre-

dominance of staphylococci and a few diplococci which could not be separated and grown in pure culture. In view of this finding we take the liberty to quote Josephine Neal^{17, 18}: "It should be understood that meningitis associated with a definite focus that is apparently primary is not necessarily secondary to it. Not infrequently we see cases of meningococcic meningitis following a pneumonia or otitis media which in all probability are not due to the meningococcus. A recent case of meningitis caused by the hemolytic streptococcus occurred during convalescence from a pneumococcus type II pneumonia." This same author¹⁷ indicates that about 34 per cent of the cases of pneumococcic meningitis which she observed up to 1934 followed infection of the mastoid area, paranasal sinuses, or middle ear. These are the most frequent foci of infection and routes of initiation of pneumococcic meningitis. However, it is also interesting to note that in this same series of cases it was observed that 23 per cent had no evidence of any primary infection elsewhere in the body.

In order of frequency of the bacteriologically etiological variety of meningitis, the meningococcus is the first; the tubercle bacillus second; the streptococcus and the pneumococcus rank third, having about the same degree of incidence. Josephine Neal¹⁸ reported 3,178 cases of meningitis which she classified according to bacteriological etiology. The meningococcus was the offending organism in 1,358 or 42 per cent of the cases, the tubercle bacillus was the offending organism in 986 or 31 per cent of the cases. The streptococcus was found in 238 cases of 7.4 per cent, and the pneumococcus was found in 235 or 7.3 per cent of the cases. The general reliability of this statistical study is borne out by the reports of various other authors.

It is interesting to note that after the age of 20,¹⁸ the incidence of pneumococcic meningitis was 38 per cent. This figure is relatively high for this age group as compared with other types of meningitis with the possible exception of the streptococcic variety. Our case concerned a 22 year old male.

It is necessary to mention that there have been cases recorded of pneumococcic meningitis which have recovered spontaneously with only supportive treatment, occasionally aided by continued spinal punctures. These cases have been so few that their incidence does not alter the available statistics which vouch for the known high mortality rate of pneumococcic meningitis.

Recent reports seem in general to indicate that sulfanilamide is not very effective in the treatment of pneumococcic pneumonia in man.¹⁹ However, experimental work shows rather conclusively that the pneumococcic organism, both in vivo and in vitro, is susceptible to a certain degree to the action of sulfanilamide.^{9, 10, 11, 12, 18, 20}

SUMMARY

Pneumococcic meningitis is a disease associated with a very high mortality rate. There have been recent reports in the literature which indicate that sulfanilamide will play an important rôle in reducing this mortality rate. A case of type XV pneumococcic meningitis complicating a right antrum sinusitis which recovered when treated by sulfanilamide and radical drainage of the sinus is reported.

CONCLUSION

Sulfanilamide therapy associated with radical drainage of foci of infection if present, we believe, is of definite value in the treatment of pneumococcic meningitis. The comparative value of sulfapyridine is in process of determination.

We wish to acknowledge thanks to Dr. Waitman F. Zinn for his permission to report this case, and to Dr. Perrin H. Long for his helpful guidance and advice in the preparation of this report.

BIBLIOGRAPHY

1. SCHWENTKER, F. F., CLASON, F. P., MORGAN, W. A., LINDSAY, J. W., and LONG, P. H.: The use of para-amino-benzene-sulfonamide and its derivatives in the treatment of beta hemolytic streptococcal meningitis, *Bull. Johns Hopkins Hosp.*, 1937, lx, 297-306.
2. ARNOLD, J. G., JR.: Treatment of hemolytic streptococcic meningitis with para-amino-benzene-sulfonamide; report of a case with recovery, *ANN. INT. MED.*, 1937, x, 1198-1204.
3. WEINBERG, M. H., MELLON, R. R., and SHINN, L. E.: Two cases of streptococcic meningitis treated successfully with sulfanilamide and prontosil, *Jr. Am. Med. Assoc.*, 1937, cviii, 1948-1951.
4. HAGEMAN, PAUL O., and BLAKE, FRANCIS G.: Clinical experience with sulphanilamide in the treatment of beta hemolytic streptococcic infections, *Am. Jr. Med. Sci.*, 1938, cxcv, 163-175.
5. TRACHSLER, W. H., FRAUENBERGER, G. S., WAGNER, C., and MITCHELL, A. G.: Streptococcic meningitis with special emphasis on sulfanilamide therapy, *Jr. Pediat.*, 1937, xi, 248-269.
6. ANDERSON, E. D.: Hemolytic streptococcic meningitis—report of a case with recovery after the treatment of prontosil and sulphanilamide, *Jr. Am. Med. Assoc.*, 1937, cviii, 1591.
7. SCHWENTKER, F. F., GELMAN, SIDNEY, and LONG, P. H.: The treatment of meningococcic meningitis with sulfanilamide, *Jr. Am. Med. Assoc.*, 1937, cviii, 1407-1408.
8. HEINTZELMAN, J. H. L., HADLEY, P., and MELLON, R. R.: Use of para-amino-benzene-sulfonamide in type III pneumococcus pneumonia, *Am. Jr. Med. Sci.*, 1937, xciii, 759-763.
9. COOPER, F. B., GROSS, P., and MELLON, R. R.: Action of para-amino-benzene-sulfonamide on type III pneumococcus infection of mice, *Proc. Soc. Exper. Biol. and Med.*, 1937, xxxvi, 148-152.
10. COOPER, F. B., and GROSS, P.: Efficacy of para-amino-benzene-sulfonamide in experimental Type III pneumococcus pneumonia of rats, *Proc. Soc. Exper. Biol. and Med.*, 1937, xxxvi, 225-227.
11. COOPER, F. B., and GROSS, P.: Para-amino-benzene-sulfonamide therapy in Type III pneumococcal pneumonia, *Proc. Soc. Exper. Biol. and Med.*, 1937, xxxvi, 678-681.
12. ROSENTHAL, S. M., BAUER, H., and BRANHAM, S. E.: Studies in chemotherapy. IV. Comparative studies of sulfonamide compounds in experimental pneumococcus, streptococcus, and meningococcus infections, *Pub. Health Rep.*, 1937, lii, 662.
13. BRANHAM, S. E., and ROSENTHAL, S. M.: Studies in chemotherapy. V. Sulfanilamide, serum, and combined drug and serum therapy in experimental meningococcus and pneumococcus infections in mice, *Public Health Rep.*, 1937, lii, 685.
14. HORLEIN, H.: The chemotherapy of infectious diseases caused by protozoa and bacteria, *Proc. Roy. Soc. Med.*, 1936, xxix, 313-324.
15. NEAL, J. B., and APPLEBAUM, E.: Experience with sulfanilamide in meningitis, *Am. Jr. Med. Sci.*, 1938, cxcv, 175-182.

16. BASMAN, JR., and PERLEY, A. M.: Report of patients treated with sulfanilamide at the St. Louis Children's Hospital, Jr. *Pediat.*, 1937, xi, 212-237.
17. NEAL, J. B., JACKSON, H. W., and APPLEBAUM, E.: A comprehensive study of meningitis secondary to otitic or sinus infection, *Ann. Otol., Rhin. and Laryng.*, 1934, xliii, 658-666.
18. NEAL, J. B.: Diagnosis and treatment of meningitis, *Med. Clin. N. Am.*, 1935, xix, 751-771.
19. LONG, PERRIN H.: Personal communication to the authors.
20. LONG, PERRIN H., and BLISS, E.: The use of para-amino-benzene-sulphonamide or its derivatives in the treatment of infections due to beta hemolytic streptococci, pneumococci and meningococci, *South. Med. Jr.*, 1937, xxx, 479-487.
21. MERTINS, P. S., SR., and MERTINS, P. S., JR.: Meningitis due to Type IV pneumococcus with recovery, *Arch. Otolaryng.*, 1937, xxv, 657-660.

EDITORIAL

PROGRESS IN ADRENAL CORTICAL HORMONE THERAPY

Thomas Addison's description (1855) of a clinical syndrome (*morbus addisonii*) which resulted from destruction of the adrenal glands first called attention to the vital function of these organs. Shortly thereafter Brown-Sequard (1856) demonstrated conclusively that complete removal of both adrenals was followed promptly by death of the experimental animal. The studies of Vulpian, Oliver, Schaeffer, Abel, Takamine and Aldrich ultimately resulted in the isolation of epinephrin from the adrenal medulla. However, treatment with epinephrin was ineffective in controlling the signs and symptoms of adrenal insufficiency. It was also observed experimentally that the complete removal of one adrenal, accompanied by destruction of the medulla of the remaining adrenal, did not give rise to the signs and symptoms of adrenal insufficiency. From these observations it appeared that the "life-maintaining" substance liberated by the adrenal was derived from the cells of the cortex.

In 1927 Hartman et al.¹ and Rogoff and Stewart² independently reported the preparation of adrenal cortical extracts which were capable, on injection, of prolonging the survival period of adrenalectomized animals. In 1930, Swingle and Pfiffner,³ and Hartman and Brownell,⁴ described methods of preparing adrenal cortical extracts of much greater potency. These extracts appeared to be capable of maintaining bilaterally adrenalectomized dogs and cats in good condition for prolonged periods. It was also noted that injections of these extracts in adequate quantities resulted in great improvement in patients with Addison's disease.^{5, 6} However, difficulties encountered in the preparation of large quantities of potent extract and in the standardization of the hormone, in addition to the high cost of the preparation, greatly limited adequate clinical trial. Thus at the Mayo Clinic, between the years of 1930 and 1933, Snell⁷ noted that the expected length of life of patients with Addison's disease was only slightly prolonged, although marked and continued improvement was observed in some patients following treatment with adrenal cortical extract. During this period it was known that adequate hormone therapy for a moderately severe case of

¹ HARTMAN, F. A., MACARTHUR, C. G., and HARTMAN, W. E.: A substance which prolongs the life of adrenalectomized cats, *Proc. Soc. Exper. Biol. and Med.*, 1927, xxv, 69.

² ROGOFF, J. M., and STEWART, G. N.: The influence of adrenal extracts on the survival period of adrenalectomized dogs, *Science*, 1927, lxvi, 327.

³ SWINGLE, W. W., and PFIFFNER, J. J.: An aqueous extract of the suprarenal cortex which maintains the life of bilaterally adrenalectomized cats, *Science*, 1930, lxxi, 321.

⁴ HARTMAN, F. A., and BROWNELL, K. A.: The hormone of the adrenal cortex, *Proc. Soc. Exper. Biol. and Med.*, 1930, xxvii, 938.

⁵ ROWNTREE, L. G., and GREENE, C. H.: The treatment of patients with Addison's disease with the "cortical hormone" of Swingle and Pfiffner, *Science*, 1930, lxxii, 482.

⁶ HARTMAN, F. A., BOWEN, B. D., THORN, G. W., and GREENE, C. W.: Vital hormone of adrenal cortex. *Ann. Int. Med.*, 1931, v, 539.

⁷ SNELL, A. M.: Diagnosis and treatment of Addison's disease with reference to series of 46 patients treated with suprarenal cortical hormone, *Internat. Clin.*, 1934, iii, 46.

Addison's disease might cost \$1,000 or more annually. It was apparent that although further improvements might be made in the extraction of the hormone from the glands it was doubtful whether the preparation of hormone from this natural source would ever provide adequate quantities at a cost which most patients could afford.

The classical studies of Loeb et al.⁸ and Harrop et al.,⁹ demonstrated the beneficial effect of sodium salts in the treatment of patients with Addison's disease, and it was evident that in the clinical evaluation of adrenal cortical hormone therapy, the mineral content of the diet must be considered carefully. Not only was a diet of high sodium content beneficial, but later work (Truszkowski and Zwemer,¹⁰ Wilder et al.¹¹) demonstrated the beneficial effect of a low potassium intake in adrenal insufficiency.

In 1933 both Kendall¹² and Grollman¹³ obtained crystalline material from adrenal cortical extracts. This material appeared to possess cortical hormone-like activity. Somewhat later Reichstein¹⁴ isolated a crystalline compound from the adrenal cortex which possessed cortical hormone-like activity and which he identified and named "corticosterone." Subsequently Kendall demonstrated the identity of his active compound with that of Reichstein's "corticosterone."

In 1937 Steiger and Reichstein announced the synthesis of a steroid compound, desoxy-corticosterone acetate, from stigmasterol.¹⁵ This compound was found to possess cortical hormone-like activity¹⁶ and was noted to be very closely related, chemically, to progesterone, a sex hormone secreted by the corpus luteum. During the following year Reichstein and Von Euw¹⁷ succeeded in isolating desoxy-corticosterone from adrenal cortical extract, thus establishing its natural occurrence. It is unique that in this instance a hormone was synthesized prior to its isolation from a natural source. It appears probable that desoxy-corticosterone is one of a group of closely related steroid compounds which possess cortical hormone-like activity.

⁸ LOEB, R. F.: Effect of sodium chloride in treatment of patient with Addison's disease, *Proc. Soc. Exper. Biol. and Med.*, 1933, xxx, 808.

⁹ HARROP, G. A., WEINSTEIN, A., SOFFER, L. J., and TRESCHER, J. H.: Diagnosis and treatment of Addison's disease, *Jr. Am. Med. Assoc.*, 1933, c, 1850.

¹⁰ TRUSZKOWSKI, R., and ZWEMER, R. L.: Cortico-adrenal insufficiency and potassium metabolism, *Biochem. Jr.*, 1936, xxx, 1345.

¹¹ WILDER, R. N., KENDALL, E. C., SNELL, A. M., KEPLER, E. J., RYNEARSON, E. H., and ADAMS, M.: Intake of potassium, important consideration in Addison's disease; metabolic study, *Arch. Int. Med.*, 1937, lxx, 367.

¹² KENDALL, E. C.: Chemical and physiological investigation of the suprarenal cortex, *Symposia on Quant. Biol.*, 1937, v, 299.

¹³ GROLLMAN, A.: Physiological and chemical studies on the adrenal cortical hormone, *Symposia on Quant. Biol.*, 1937, v, 313.

¹⁴ REICHSTEIN, T.: Chemie des Cortins und seiner Begleitstoffe, *Ergebn. d. Vitamin- u. Hormonforsch.*, 1938, i, 334.

¹⁵ STEIGER, M., and REICHSTEIN, T.: Desoxy-cortico-steron (21-oxy-progesteron) aus Δ^5 -3-Oxy- Δ^4 -cholensäure, *Helvet. chim. acta*, 1937, xx, 1164.

¹⁶ THORN, G. W., ENGEL, L. L., and EISENBERG, H.: Effect of corticosterone and related compounds on renal excretion of electrolytes, *Jr. Exper. Med.*, 1938, lxxviii, 161.

¹⁷ REICHSTEIN, T., and v. EUW, J.: Ueber Bestandteile der Nebennierenrinde. Isolierung der Substanzen Q (Desoxy-corticosteron) und R sowie weiterer Stoffe, *Helvet. chim. acta*, 1938, xxi, 1197.

The close chemical relation between desoxy-corticosterone (21-hydroxyprogesterone, a compound having a high degree of activity as measured by its ability to maintain adrenalectomized animals in good condition) and progesterone, a female sex hormone, is of great interest. The similarity in the clinical picture produced by certain tumors of the adrenal cortex and by arrhenoblastomata of the ovary is well known. Furthermore it has been shown recently¹⁸ that injections of crystalline progesterone result in a retention of sodium and chloride, and an increased renal excretion of potassium. This effect is quite similar to that observed following injections of adrenal cortical hormone.¹⁶ It is also of interest to note that the lives of adrenalectomized animals have been prolonged by injecting large doses of progesterone.¹⁹ No other sex hormone appears to be of any benefit in prolonging the survival of adrenalectomized animals. It thus appears that not only are the adrenal cortical hormone and progesterone closely related chemically but there is also some overlapping in the physiological effects of these compounds.

Intramuscular injections of synthetically prepared desoxy-corticosterone acetate have been shown to be extremely useful in the treatment of patients with Addison's disease.²⁰ Treatment with desoxy-corticosterone acetate was associated with an increase in body weight, an elevation of blood pressure, increase in plasma volume, a restoration of the plasma concentrations of sodium, chloride and potassium to normal levels, a positive sodium and chloride balance, an increased renal excretion of potassium and inorganic phosphorus, and improved muscular strength. Desoxy-corticosterone acetate treatment was also associated with some improvement in carbohydrate metabolism as measured by a return of the glucose tolerance test to normal.²¹ However, in most patients the fasting blood sugar levels remained low despite continued hormone therapy. No striking changes were observed in the pigmentation of patients treated with synthetic hormone.

Desoxy-corticosterone appears to be the most active of the crystalline compounds thus far isolated from the adrenal cortex as measured by the quantity necessary to maintain adrenalectomized animals. The potency of this compound in promoting the storage of glycogen in the liver,²² and in preventing the development of muscular fatigue under certain experimental conditions,²³ is less than that of other closely related steroid com-

¹⁸ THORN, G. W., and ENGEL, L. L.: Effect of sex hormones on renal excretion of electrolytes, *Jr. Exper. Med.*, 1938, lxxviii, 299.

¹⁹ GAUNT, R., and HAYS, H. W.: Life-maintaining effect of crystalline progesterone in adrenalectomized ferrets, *Science*, 1938, lxxxviii, 576.

²⁰ THORN, G. W., HOWARD, R. P., and EMERSON, K., JR.: Treatment of Addison's disease with desoxy-corticosterone acetate, a synthetic adrenal cortical hormone (preliminary report), *Jr. Clin. Invest.*, 1939, xviii, 449.

²¹ THORN, G. W., HOWARD, R. P., EMERSON, K., JR., and FIROR, W. M.: Treatment of Addison's disease with pellets of crystalline adrenal cortical hormone (synthetic desoxy-corticosterone acetate) implanted subcutaneously, *Bull. Johns Hopkins Hosp.*, 1939, lxiv, 339.

²² LONG, C. N. H.: Personal communication.

²³ INGLE, D. J.: Personal communication.

²⁴ DEANESLY, R., and PARKES, A. S.: Factors influencing effectiveness of administered hormones, *Proc. Roy. Soc. London, s. B*, 1937, cxxiv, 279.

pounds obtained from the adrenal cortex. It also appears as though adrenal cortical extracts may contain compounds of much greater activity than those thus far isolated.¹²

The synthesis of desoxy-corticosterone provides for the first time an adequate quantity of crystalline adrenal cortical hormone for clinical use. The uniformity of the preparation, and the constancy of potency are of inestimable value, but not more important than is the fact that the synthetic compound provides adequate therapy at a greatly reduced cost.

Recently a method has been described,²¹ whereby prolonged hormone therapy may be obtained by implanting subcutaneously tablets of crystalline desoxy-corticosterone acetate in patients with Addison's disease. This method is an application of the experimental studies of Deanesly and Parkes who obtained a prolonged hormone effect when crystals of sex hormones were implanted in the subcutaneous tissues of suitable animals.²⁵ In preparing a patient for the implantation of pellets, it is essential to determine beforehand the dose of synthetic hormone in oil, injected intramuscularly once daily, which is necessary for satisfactory maintenance. From the daily hormone requirement, the number of tablets (100-150 mg. each) necessary to provide adequate substitution can then be calculated. The hard tablets of synthetic hormone, being only slightly water soluble are absorbed slowly and provide a supply of hormone for several months. They have been removed from time to time, and since no binding substance is used, an accurate measure of the amount of hormone absorbed was ascertained simply by drying and then weighing the tablets. It was found that over a period of several months there was an almost uniform rate of absorption. No untoward local reaction occurs about the tablets. This method of therapy offers several advantages in that daily injections of hormone are obviated, the absorption of hormone occurs at a much more constant rate, and a considerable economy in hormone is effected (approximately 30 per cent) as compared to the hormone required when single daily intramuscular injections of hormone are employed.

It is to be noted, however, that whereas aqueous extracts of adrenal cortex can be given in almost unlimited quantities with no apparent untoward reaction the marked sodium chloride retaining property of desoxy-corticosterone acetate permits the development of edema and hypertension when the hormone is administered in excess, particularly when added sodium chloride therapy is given simultaneously.

The synthesis of desoxy-corticosterone acetate marks a new step in the study of the hormone of the adrenal cortex and in the treatment of patients with Addison's disease. The uniform potency of the preparation will be of inestimable aid in controlling adequate therapy. The subcutaneous implantation of pellets of hormone offers a very advantageous method of administering hormone where long continued therapy is necessary.

G. W. THORN

REVIEWS

Adventures in Respiration: Modes of Asphyxiation and Methods of Resuscitation. By YANDELL HENDERSON. 316 pages; 21 × 14.5 cm. The Williams & Wilkins Company, Baltimore. 1938. Price, \$3.00.

To the average internist this will be both a stimulating and a disturbing book. It attacks his conceptions of acidosis, its definition, its mechanism, and the validity of the usual methods of measuring it. In return it leaves him with a new theory which is rather difficult to grasp. The inner relationship of oxygen deficiency to carbon dioxide deficiency has not yet been solved.

The book is to some extent historical, even autobiographical in its approach, since it tells the story of the growth of our knowledge of respiration over 30 years during which the author has been working in this field. In this time he has registered many successes and of course a few failures. We owe to him the widespread acceptance of inhalations of carbon dioxide and oxygen as an indispensable aid in resuscitation from asphyxia and in postoperative depression. His chapter on the use of the same remedy in pneumonia reveals that he is not yet willing to concede that in this condition it has proved a failure.

A disadvantage of the book is that while the author's opponents are brilliantly attacked and his own position interestingly stated there are not enough data furnished to enable a careful reader to form his own opinion. It would seem helpful, too, to the general scientific public, for whom the book seems to have been written, if the author would somewhere clearly state just what his own definition of acidosis is and give us some factual basis for the intriguing phrase "the flight of alkali to the tissues."

In spite of the confusion it induces in the uninitiated, no physician can fail to be attracted by the enthusiasm of the author, nor by his persuasiveness, his ingenuity, and the modest story of his frequent triumphs.

M. C. P.

Outline of Psychiatric Case-Study. By PAUL W. PREU, M.D. 140 pages; 19 × 13 cm. Paul B. Hoeber, Inc., New York City. 1939. Price, \$1.85.

This outline seems essentially an expansion of the well-known, standard Kirby and Cheney Guide. Dr. Preu indicates most of the questions he considers necessary to obtain adequate information about an individual. He very wisely stresses the importance of putting things down in the terms actually used by the patient and the informant—not the historian's retrospective impression of what was said.

The observations on history-taking technic (pp. 4-6) and method of mental examination (pp. 74-76) are good, although we do feel that the mental examination should contain only items directly observed at that time by the examiner (p. 81).

Too much stress is laid on school record as a criterion of intelligence. We should like to have seen a section on the examination of uncoöperative patients included. We dislike the use of such obscure terms as "anancasm" (none of our dictionaries listed it).

It is very easy to read. Like most guides, it should be most useful in making the historian think about things he wants to know about a well studied case. Its skeleton outlines for practical use (no one could possibly sit down with it at a history-taking session) are a little lost in the mass of questions. It is a good guide for institutional beginners. But we wish someone, sometime, would devise a satisfactory outline of mental examination for non-psychotic, office and general hospital patients.

H. M. M.

The Avitaminoses. By WALTER H. EDDY, Ph.D., and GILBERT DALLDORF, M.D. 338 pages; 23.5 × 15.5 cm. The Williams & Wilkins Company, Baltimore. 1937. Price, \$4.50.

The book plans to be a helpful manual rather than a complete treatise on the avitaminoses and it well fulfills its purpose. The clinician will find an authoritative statement of the nature of the vitamins and of their function. Rapid changes in this field have already added many new facts not available when the book was published but this small volume will long remain a valuable basic text for the internist.

M. C. P.

Diseases of the Nervous System in Infancy, Childhood, and Adolescence. By FRANK R. FORD, M.D. 939 pages; 25.5 × 16.5 cm. Charles C. Thomas, Springfield, Illinois. 1937. Price, \$8.50.

This volume of 939 pages appeared two years ago but has not previously been reviewed in this journal. It has stood the test of these years in which it has been frequently used as a reference book. It is a careful scholarly type of work of unusual completeness, clearly written, practical, and illustrated by numerous case histories. To the internist and pediatrician it is a great source of help in a field which cannot be sharply separated from their own. This help will be particularly in the clinical descriptions of the disease entities and in the discussions of diagnosis. Treatment is often dealt with rather briefly and sometimes without the specific details which a practitioner craves. The well chosen references will be of great assistance. Those who have not used this text will be well repaid if they learn to consult it.

M. C. P.

Manual of Toxicology. By FORREST RAMON DAVISON, M.B., M.Sc., Ph.D. 241 pages; 19 × 13.5 cm. Paul B. Hoeber, Inc., New York City. 1939. Price, \$2.50.

This manual cannot be commended. The clinical effects of the chief poisons have been very inadequately and often incorrectly described. The therapeutic procedures are vaguely indicated, so that no safe application of the measures advocated could be deduced. Many important therapeutic measures are omitted. Minor disadvantages are the frequent misspelling of words and the incompleteness of the index.

C. A.

COLLEGE NEWS NOTES

THE NEW 1939 DIRECTORY OF THE COLLEGE

By October 1 a new and completely revised Directory of the American College of Physicians will be ready for distribution. It includes the names of 1 Master, 2969 Fellows and 1234 Associates; total 4204. The contents of the Directory include Officers and Regents, past Officers, past Boards of Regents, Board of Governors, Committees, a historical statement concerning the College, the Constitution and By-Laws, Directory of Life Members and statement concerning the Endowment Fund, record of Awards and Fellowships, Geographic Roster of all members, Alphabetical and Biographical Roster of all members and a directory of Deceased Members. This book is used extensively as a directory of competent internists and allied specialists on the North American Continent. All members of the College in good standing receive the Directory complimentary, as a part of their memberships. Members with waiver of dues, because of age limit or retirement from practice because of illness or other reasons, may obtain copies of the Directory at the pre-publication price of \$1.25 postpaid. The Directory is not sold for commercial purposes. However, it is frequently complimented to libraries, Deans of Medical Schools, to Research organizations and to Municipal, State and National scientific bodies.

1940 ANNUAL SESSION OF THE COLLEGE

The Twenty-fourth Annual Session of the American College of Physicians will be held in Cleveland, Ohio, April 1-5, inclusive, 1940, with General Headquarters at the Municipal Auditorium and Hotel Headquarters at the Statler Hotel.

Exceptionally fine facilities are available at the hotels, the auditorium and in the hospitals. Cleveland groups and institutions, including Western Reserve University School of Medicine, are placing all facilities at the disposal of the College.

The programs for the General Sessions and the Special Lectures are in charge of the President of the College, Dr. O. H. Perry Pepper, 36th & Spruce Sts., Philadelphia, Pa. All requests and suggestions for papers on the General Sessions program, or on the Lecture Program, should be addressed to President Pepper. The program of Clinics and Round Tables is under the direction of the General Chairman, Dr. Howard T. Karsner, Institute of Pathology, Western Reserve University, Cleveland, Ohio. The Technical Exhibits and General Business Management of the Session will be under the direction of the Executive Secretary, Mr. E. R. Loveland, 4200 Pine St., Philadelphia, Pa.

Dr. David P. Barr, F.A.C.P., St. Louis, was a guest speaker before the 47th Annual Meeting of the Idaho State Medical Association at Boise, August 23-26, his subjects being "Influence of the Pituitary Gland on Bodily Function and Disease"; "Clinical Management of Lobar Pneumonia"; "Vitamins and Their Clinical Importance"; "Diagnosis and Treatment of Parathyroid Disease."

Dr. James D. Bruce, F.A.C.P., President-Elect of the American College of Physicians and Vice President in charge of Postgraduate Medical Education of the University of Michigan Medical School, and Dr. Stuart Pritchard, F.A.C.P., Director of the W. K. Kellogg Foundation, Battle Creek, are among members of the newly formed Michigan Poliomyelitis Commission to arrange consultation service for the

early diagnosis and prompt orthopedic care of patients in the recent outbreak of infantile paralysis. The Commission received \$10,000 from the Michigan State Medical Society, Michigan Crippled Children's Commission, Michigan Society for Crippled Children, the Children's Fund, the Kellogg Foundation and the Wayne County Board of Auditors. The State was organized into sixteen districts in which consultation service was maintained. County, State and District Health Officers acted as clearing agents in obtaining consultants. The Presidents of County Medical Societies arranged for the service in those counties that do not have full-time health service. Eighty-six cases were reported the first ten days in August, sixty-two of these being in Detroit.

A recent announcement from New York University College of Medicine contains advice of the following faculty promotions:

Dr. Currier McEwen, F.A.C.P.
 Dr. Elaine P. Ralli, F.A.C.P.
 Dr. William Goldring, F.A.C.P.
 Dr. Norman H. Jolliffe, F.A.C.P.

promoted to Associate Professors of Medicine;

Dr. Morris Block (Associate)
 Dr. Marshall S. Brown, Jr. (Associate)

promoted to Assistant Professors of Clinical Medicine.

Among guest speakers on the program of the Fifth Annual Piedmont Postgraduate Clinical Assembly at Anderson, S. C., September 19-21, were the following members of the College:

Dr. Kenneth M. Lynch, F.A.C.P., Charleston, S. C., "Some Things We Know About Cancer";
 Dr. Edgar R. Pund, F.A.C.P., Augusta, Ga., "Ovarian Tumors";
 Dr. Virgil P. Sydenstricker, F.A.C.P., Augusta, Ga., "Incomplete Deficiency Syndromes";
 Dr. Robert Wilson, Jr., F.A.C.P., Charleston, S. C., "Diabetes and the Use of Protamine Insulin."

Dr. James S. Sweeney, F.A.C.P., Dallas, Texas, was the recipient of the honorary degree of Doctor of Laws at the last commencement of Texas Christian University.

Dr. David B. Snelling (Associate), Montgomery, Ala., has been appointed Health Officer of Choctaw (Ala.) County.

Dr. Gerald B. Webb, F.A.C.P., 2nd Vice President of the American College of Physicians, received the Trudeau Medal of the National Tuberculosis Association at its last Annual Meeting in Boston. Dr. Webb received the award in recognition of his attempts "to produce specific immunity against tuberculosis by the inoculation of animals with very minute numbers of tubercle bacilli."

The Institute of Medicine of Chicago recently announced again the offering of the Joseph A. Capps (F.A.C.P.) Prize of \$400 for the most meritorious investigation in medicine, or in the specialties in medicine. Competition is open to graduates of medical schools in Chicago, who have completed an internship, or a year of laboratory work, since the first of 1937. Manuscripts must be submitted to the Secretary of the Institute, 86 East Randolph St., Chicago, Ill., not later than December 31.

Dr. Cyrus C. Sturgis, F.A.C.P., Professor of Internal Medicine and Chairman of that department, University of Michigan Medical School, Ann Arbor, and Dr. John E. Gordon, F.A.C.P., Professor of Preventive Medicine and Epidemiology, Harvard University Medical School, Boston, have been appointed special consultants for the W. K. Kellogg Foundation, Battle Creek.

Dr. William W. Graves, F.A.C.P., Professor of Neuropsychiatry and Director of that department, St. Louis University School of Medicine, has been selected to receive the Award of Merit of the St. Louis Medical Society, "in consideration of the results of his studies on inherited variations in relation to the problems of the human constitution."

Under the Presidency of Dr. Charles E. Sears, F.A.C.P., Portland, the Oregon State Medical Society held its 65th Annual Meeting in Gearhart, September 6-9. Dr. Clifford J. Barborka, F.A.C.P., Chicago, appeared on the program with three addresses:

"Recent Advances in Nutrition";
"Management and Treatment of Obesity";
"Diagnosis and Treatment of Peptic Ulcer."

Dr. Paul H. Ringer, F.A.C.P., Asheville, N. C., and Dr. David O. N. Lindberg, F.A.C.P., Decatur, Ill., have been elected Vice Presidents of the National Tuberculosis Association.

Dr. James Burns Amberson, Jr., F.A.C.P., New York, Dr. Lewis J. Moorman, F.A.C.P., Oklahoma City, Okla., and Dr. Benjamin L. Brock, F.A.C.P., Waverly Hills, Ky., have been elected President, President-Elect and Secretary, respectively, of the American Trudeau Society. This Society was organized in 1905 as the American Sanatorium Association, but at its Annual Meeting in Boston in June, its name was changed and its scope and functions expanded. While primarily the membership was made up of physicians associated with sanatoriums, the reorganization provides for inclusion of many physicians outside of sanatoriums, who have active interest in tuberculosis and other diseases of the chest.

OBITUARIES

DR. LOUIS H. FLIGMAN

Dr. Louis H. Fligman of Helena, Montana died July 14, 1939, following an appendix operation performed July 4.

He was born in Rumania in 1878, coming to the United States as a boy. He resided in Minneapolis, where he had his preliminary education, graduating from the University of Minnesota in medicine in 1901. Dr. Fligman moved to Helena, Montana, where his interest in internal medicine and his unusual diagnostic skill soon earned for him a place of enviable distinction which extended well beyond the confines of his own state.

Dr. Fligman became a member of the American College of Physicians February 24, 1920, and a life member in January, 1938; was elected to the Board of Governors in 1925, serving continuously in that capacity until his death. His interest in the College was manifested by consistent attendance of the sessions as well as the Board meetings. He was also a former President of the Montana Medical Association as well as a member and former President of the State Board of Health.

He was attending physician to St. Peter's and St. John's Hospitals, consulting internist to the Veterans Administration Facility, Lieutenant Commander in the Reserve Corps of the United States Navy, Director for the Montana American Society for the Control of Cancer, and was a diplomate of the American Board of Internal Medicine.

His postgraduate studies were pursued with unusual zeal, and on eight occasions he returned to Vienna for postgraduate study. Dr. Fligman was most energetic in the pursuit of outdoor exercise, and was an ardent golfer, being a member of the Helena Town and Country Club. His local interests embraced membership in the Chamber of Commerce and the Mountain Club. A most able and accomplished physician, despite his remoteness from medical centers, he was rarely equipped and qualified to practice internal medicine. His diagnostic skill was exceptional, while his unselfishness and fine standard of ethics were outstanding.

He is survived by his widow; a brother, Mr. Jos. Fligman of Chicago; a sister, Mrs. J. S. Holzman of Helena; and one step-daughter, Mrs. Donald C. McGraw of Summit, N. J.

CHARLES H. COCKE, M.D., F.A.C.P.
Chairman of the Board of Governors, A.C.P.

DR. JAMES FRANCIS RICE

Dr. James Francis Rice, Fellow of the College since 1917 and, therefore, almost a charter member, died on August 3, 1939, at his home in Watertown, N. Y., from a cerebral hemorrhage. He was born in York,

Pa., on September 3, 1872, a son of Rev. Dr. William Henry Rice and Mary Holland Rice. His ancestors were among the early settlers in America and were among the founders of Bethlehem, Pa. He attended Central High School in Philadelphia, Pa. He received his A.B. degree from New York University in 1893 and his A.M. degree from that University in 1895. From 1894 to 1898 he was a teacher at the New York School for the Blind in New York City. He then entered the College of Physicians and Surgeons, Columbia University, from which he was graduated in 1902 with a degree of Doctor of Medicine. From 1902 to 1904 he was an interne in the New York Hospital. He spent some time in service at the Westchester Division of the New York Hospital, then later in 1904 he began his private practice in Buffalo, and continued his practice there until the fall of 1935, when he went to Watertown, where he was on the Associate Staff of both the Mercy Hospital and the House of the Good Samaritan.

Dr. Rice married Miss Grace M. Easterly of Watertown, N. Y., in August 1925. She survives, as does a sister of Dr. Rice, Miss Rebekeh Rice of Randolph, N. Y. He was a member of various medical bodies. While in Buffalo he was from 1921 to 1925 secretary and later from 1930 to 1931 president of the Buffalo Academy of Medicine. He was also a Fellow of the Academy. He was a member of Psi Upsilon fraternity and served as president of the Buffalo Alumni Chapter. He was also a member of the New York State Medical Association and the Jefferson County Medical Society. He had also served as president of the Buffalo Society of Phi Beta Kappa.

CHARLES F. TENNEY, M.D., F.A.C.P.,
Governor for Eastern New York

ANNALS OF INTERNAL MEDICINE

VOLUME 13

OCTOBER, 1939

NUMBER 4

CULTURE OF HUMAN MARROW; STUDIES OF THE EFFECTS OF ROENTGEN-RAYS *

By EDWIN E. OSGOOD, M.D., and GEORGE J. BRACHER, M.D.,
Portland, Oregon

THE monographs on the biologic action of roentgen-rays by Duggar¹ and Scott² and on the effects of roentgen-rays on the blood and blood-forming organs by Selling and Osgood³ should be consulted for a review of the literature.

Most of the research on the action of roentgen-rays has been done on insect eggs, lower animals or plants and those studies which have been made on human material have necessarily not been quantitative nor adequately controlled. Much of this research has been done with doses far above any that are ever used in clinical therapy. Scott, therefore, very logically states:

(1) When any tissue is irradiated, careful measurement, both physical and biological, should be recorded. This may appear an obvious necessity, but neglect of the quantitative aspect of the biological action of radiations has been largely responsible for the errors, misunderstandings and controversies that are so apparent in the existing literature of the subject.

(2) More information about the processes by which cells recover from the effects of radiations, information which can be gathered by the experimental investigation of the time-factor, would be of immediate practical importance in radio-therapy.

(3) There is little knowledge about the physiology of the process of cell division. The study of the action of drugs on cell division and on the radio-sensitivity of cells seems likely to yield fundamental information, not only about the action of X and γ rays but also about the process of growth itself.

The development of the marrow culture method⁴ of growing human cells has made possible the application of controlled quantitative studies to living human cells.

* Read at the New Orleans meeting of the American College of Physicians, March 27, 1939 and at the Chicago meeting of the American Roentgen-Ray Society, Sept. 22, 1939.

From the Division of Experimental Medicine and the Department of Roentgenology, University of Oregon Medical School, Portland, Ore.

This work was made possible by a grant from J. Guy Strohm, M.D., Head of the Division of Urology, University of Oregon Medical School.

With the technical assistance of Evelyn A. Packham.

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METHOD

A lead lined box (figure 1) was constructed with seven compartments just fitting the 30 c.c. vaccine vials containing the marrow. The box had two lead covers, one solid and one with an orifice the shape of a cross section of the 30 c.c. vials. These covers slide in a groove so that one vial may be exposed at a time while the others are protected. The effective-

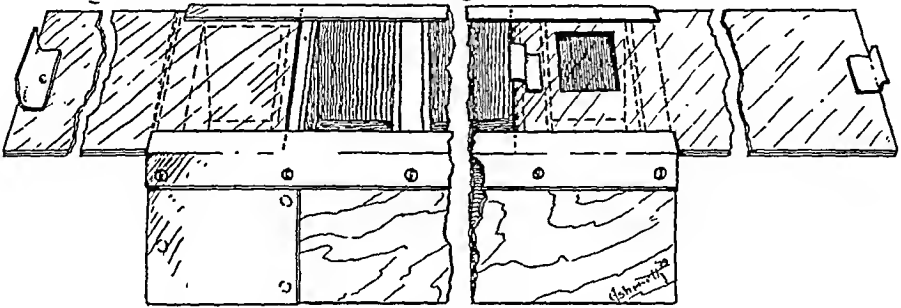


FIG. 1. Diagram of the box in which the vials containing marrow cultures were irradiated. There were 7 compartments, only 4 of which are shown. The sliding lead covers, of course, touched each other over a partition between 2 compartments while irradiation was given.

ness of this protection was tested by placing a dental film in the compartment with the control. The uniformity of the vials was tested by placing them side by side on a roentgen-ray film and taking a roentgenogram with low penetration. They gave shadows of uniform density which were less dense than those cast by the bones of the hand. The standardization of the dosage was made by E. D. Trout of the General Electric X-Ray Corporation. The actual r dosage was determined for each voltage, distance and filter used by placing the thimble ionization chamber inside of one of the vials the bottom of which had been cut off. Tests were made with the vial surrounded on three sides by lead of the same thickness as that in the box, with a layer of aluminum between the lead and the vial, and with the ionization chamber outside of the vial. These three methods gave almost identical results with the wave lengths employed, indicating that there was no appreciable absorption by the glass or scattered radiation from the lead or glass which would reach the cells.

About 10 c.c. of marrow were obtained from each subject by the technic of sternal puncture⁵ and the culture was prepared in a 50 c.c. vaccine vial as previously described.⁴ As a rule, about 50 c.c. of culture containing 2,000 nucleated cells per cu.mm. were obtained from one subject. The cultures contained both the mature and immature cells of the granulocyte series and the known highly radio-sensitive lymphocytes. The culture was thoroughly mixed and initial total and differential nucleated cell counts were done from which the absolute numbers of each cell type present were computed. Equal volumes, usually about 8 c.c., of the thoroughly mixed culture were then transferred to 30 c.c. vaccine vials which were handled

identically with the exception of the irradiation or colchicine. The controls were placed in the lead box along with the vials to be irradiated so that they were always side by side as well as being in and out of the incubator for the same lengths of time. At intervals samples were removed, the total and differential cell counts were repeated, and the absolute numbers of each cell type present were computed. In the early experiments leukocyte counting technic and a differential count of 500 to 1000 cells were used. In the later experiments, to reduce the counting error, the spinal fluid technic of counting was used and enough cells were included in the differential count so that at least 20 of the least numerous cell type were counted. This sometimes involved a differential count of several thousands of cells. The absolute number of each type of cell in the irradiated vials and in those containing colchicine was then calculated in percentage of the number of the same cell type in the control vial at the same time. The percentage and the time after irradiation were then plotted on graph paper as shown in figures 2 to 5. This method of presenting the results makes it possible to see at a glance the effects of the variable introduced since any deviation from the 100 per cent line represents a deviation from the corresponding count in the control. Actually, the effects of several variables on each cell type could be studied on cultures from one marrow but for clarity of presentation one variable will be discussed at a time and in the figures only a few cell types are included.

THE EFFECTS OF THE SAME DOSE AND WAVE LENGTH OF IRRADIATION ON THE DIFFERENT CELL TYPES *

Figure 2 shows the effects on the different cell types. Note that the fall in lymphocyte count begins early and that the decrease in lymphocytes is more rapid than in other cell types. The decrease in lymphocytes apparently begins immediately and gives a straight line curve, starting at the time of irradiation and levelling off again rather abruptly after an interval of time varying with the dose employed. The greater sensitivity of the lymphocytes was noted in all the 42 experiments which would test the relative sensitivity of the different cell types. The progranulocytes (promyelocytes) were the next most sensitive cells studied, but in none of the marrows investigated were granuloblasts (myeloblasts) numerous enough so that a count of statistically significant numbers was feasible. In most of the experiments the drop in progranulocytes (promyelocytes) occurred very early, but not enough counts were obtained in the first 12 hours after irradiation to be certain whether the curve of the fall is a straight line from the 0 time or whether, as appears in the experiment illustrated in figure 2, the count remains constant for a few hours before the fall begins. It is certain, however, that the decrease begins within the first 24 hours and con-

* The criteria of cell identification and the nomenclature used are described and illustrated in OSGOOD, E. E., and ASHWORTH, CLARICE M.: *Atlas of Hematology*, 1937, pp. 255, J. W. Stacey, Inc., San Francisco.

tinues for two to six days. The granulocytes (myelocytes) do not begin to fall until after 48 hours and then decrease gradually over a period of several days. The metagranulocytes (metamyelocytes) begin to decrease

EFFECTS OF SAME DOSE OF X-RAYS ON DIFFERENT CELL TYPES

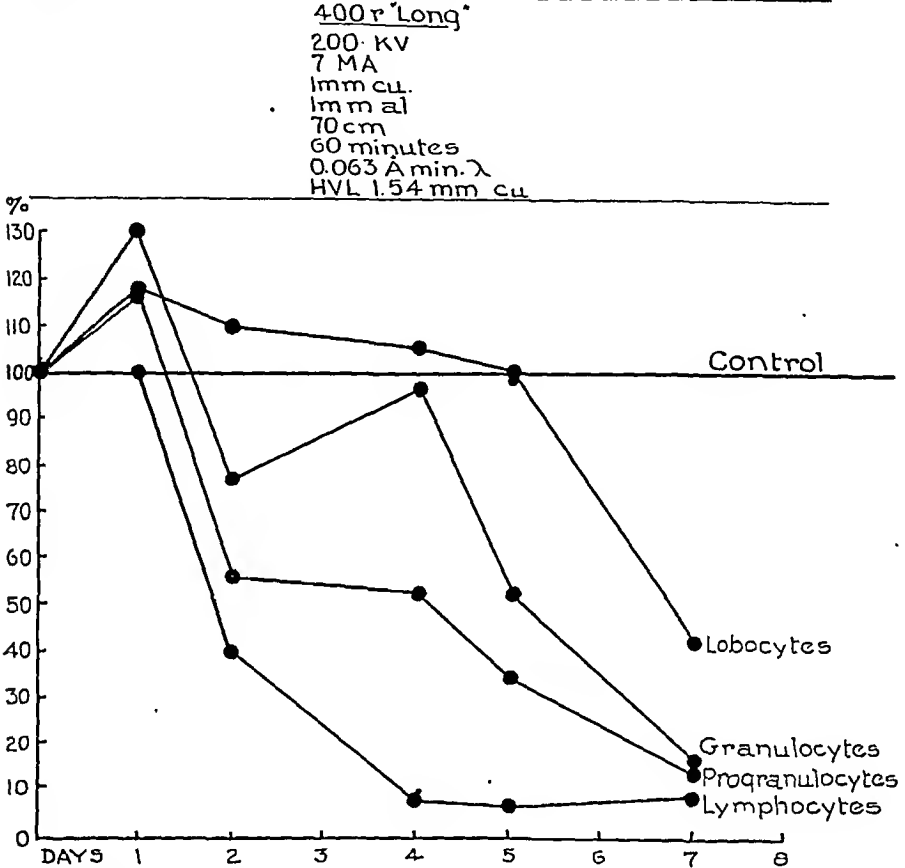


FIG. 2. In this and all subsequent figures, the curves represent actual results from a single experiment and are not averaged or smoothed. Any deviation from the 100 per cent line represents a deviation from the count for the corresponding cell type in the control examined at the same time. Smoothed curves for lymphocytes would probably show a straight line drop from 0 time similar to that shown in figure 3. Smoothed curves for progranulocytes (promyelocytes) would show a straight line drop beginning at or near 0 time but not as steep as for lymphocytes. The more mature cells of the granulocyte series in smoothed curves would show a straight line drop, leaving the 100 per cent line at progressively longer intervals after the beginning of irradiation the more mature the cell.

at about three days and the rhabdocytes (staff cells) begin to decrease at about four days, but these were omitted from the figure for the sake of clarity. The lobocytes (polymorphonuclears) begin to decrease at about five days. It is evident, therefore, that the lymphocytes are more sensitive than the other cells, and in the granulocyte series the effect is first observed on the more immature cells and later becomes manifest on the more mature cells. It is noteworthy that there was not a sudden initial drop and then a levelling off, nor was there any great increase over the control in the

numbers of disintegrating cells, as would have been the case if roentgen-rays directly killed the cells.

THE EFFECTS OF VARYING THE DOSE OF IRRADIATION

When all of the factors were kept constant and the total dose was varied by varying the time alone, results similar to those illustrated in the experiment shown in figure 3 were obtained. Fifteen marrow cultures were

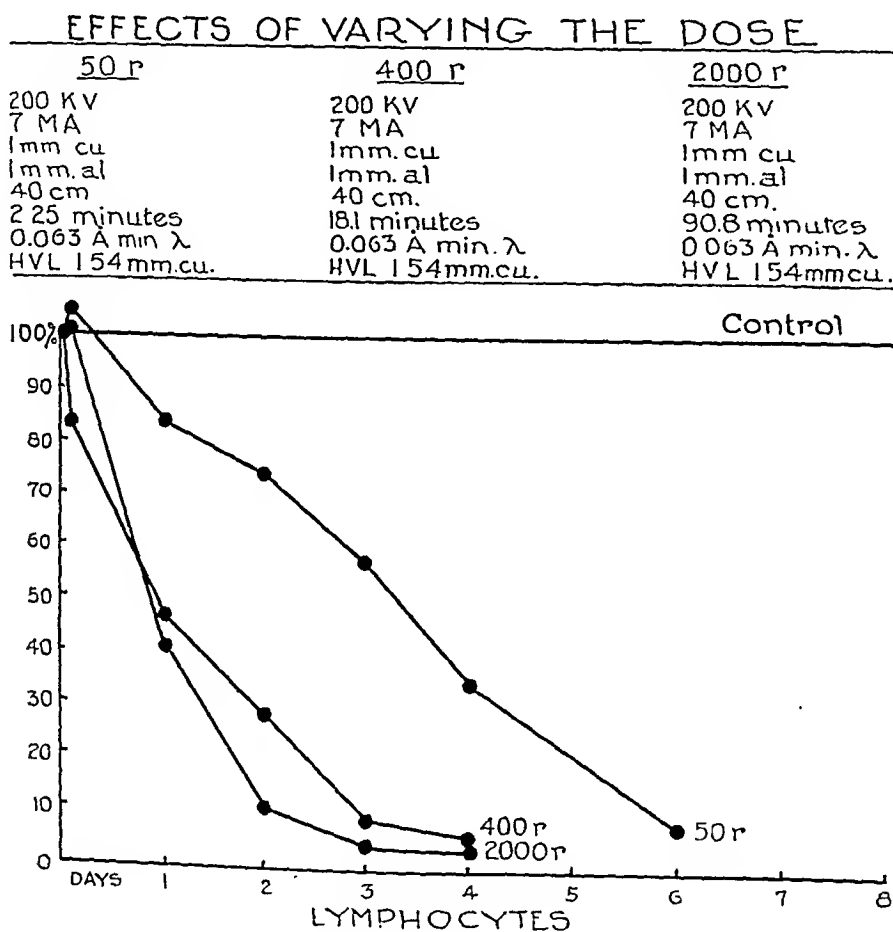


FIG. 3. Curves for the other types of cells had the same shape as illustrated and described in figure 2 and showed a similar difference with alteration in dose to that shown for lymphocytes. Note that there is a significant difference with variations in dose but that it is not directly proportional to the size of the dose.

studied on which the effects of two or more different doses of irradiation could be compared. The doses studied were 50, 75, 150, 300, 400, 500, 600, 1,000, and 2,000 r. Note that all of these doses are within the range of dosage used in treating human disease. In all the results were similar to those shown in the experiment illustrated in figure 3; namely, that within this range increasing the dose increased the effect by making the slope of the curve more steep but that the increase was not directly proportional to the dose. The quantitative effectiveness was not calculated as has been done

for insect eggs because of the great effect of the time after exposure on the number of cells remaining and the fact that most experiments did not continue longer than six or seven days when the cell counts were still decreasing. Experiments are under way to determine what levels are finally attained. It seems probable that the effects will vary with the square root of the dose as has been shown to be true for other cells. Enough work has been done to show that at least with the smaller doses there is a tendency for the cell counts eventually to become constant as shown in figure 3. The time at which this occurs varies for the different cell types and also for the different doses of irradiation. Doses as small as 50 r produce definite effects and doses of 2,000 r produce somewhat more effect than 1,000 r, so that it is evident that investigation of smaller and larger doses is needed before the minimal effective dose or the dose that produces a maximum effect on these cells can be stated.

Even when a dose of 2,000 r was used it did not result in the death of all the cells. Some of the lymphocytes survived a dose of 2,000 r although most disappeared after a dose of 50 r. Even with a dose of 2,000 r a significant fall in the numbers of lobocytes (polymorphonuclears) was not noted within the first four days. To find out whether the cells which, because of their normal morphology, were being counted as lobocytes (polymorphonuclears) and rhabdocytes (staff cells) were actually living, staphylococcus vaccine was added to the specimens removed from the cultures just before making the smears for differential counting and the percentage and absolute numbers of lobocytes (polymorphonuclears) and rhabdocytes (staff cells) containing phagocytosed cocci were compared with the corresponding values in the control. In both control and irradiated cultures, over 85 per cent of the lobocytes (polymorphonuclears) contained organisms. This was true even when the marrow had received a dose of 2,000 r until the fourth day when the lobocyte (polymorphonuclear) count had begun to fall. The slope of the curve for the cells containing phagocytosed organisms in percentage of the corresponding control cells was the same within the experimental error of the method. It seems justifiable to conclude from this that even a dose of 2,000 r does not kill lobocytes (polymorphonuclears). One of us has shown⁶ that the length of life of the lobocytes (polymorphonuclears) averages only 60 hours and varies from 48 to 90 hours so that the lobocytes (polymorphonuclears) present at the time of irradiation would all have lived out their life span before a drop in lobocytes (polymorphonuclears) began.

THE EFFECT OF VARYING THE WAVE LENGTH

Varying the wave length within the limits used (figure 4), keeping the dose in r units constant, did not produce any significant differences in results. However, only five experiments were done and the hardest and softest rays used were those shown in the figure. The whole range of wave lengths,

up to gamma rays of radium and down to grenz-rays, remains to be investigated.

THE EFFECT OF VARYING THE TIME

The effects of varying the time, keeping the total dose constant by varying the distance of the tube, are illustrated by the experiment shown in

EFFECTS OF VARIATION IN WAVE LENGTH

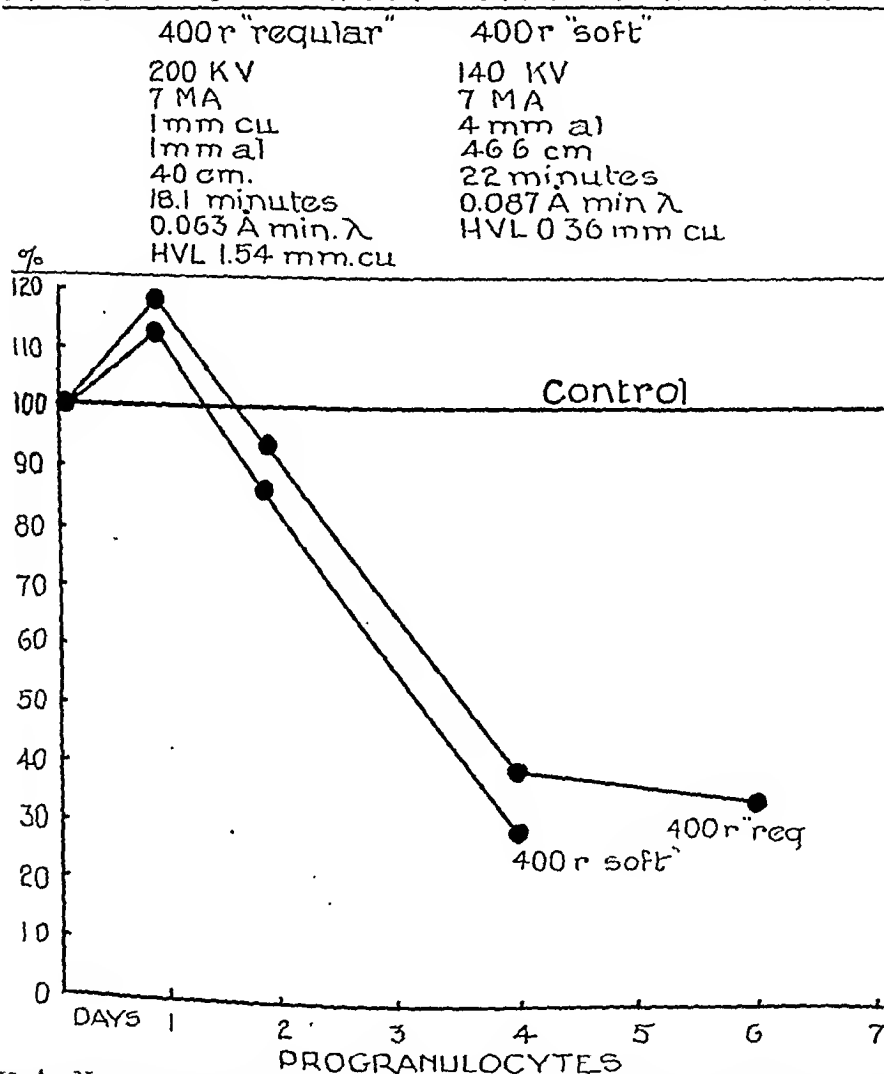


FIG. 4. Note that the same dose given at widely different wave lengths shows no significant difference in effect. This applied to the other cells studied as well as to the progranulocytes (promyelocytes).

figure 5. Within the time range of 5 to 60 minutes which was the greatest difference employed, no significant differences in effect were noted with either 400 r or 50 r. However, further work with greater differences in time of exposure, varying from the time used in radium therapy down to the minimum time in which an equivalent dose of roentgen-rays may be given with the most powerful equipment, should be investigated.

THE EFFECT OF FRACTIONAL EXPOSURES

Only one experiment on this has been completed and in this only two exposures were made about six hours apart, using doses of 200 r and 200 r with the factors shown in figure 5. No significant differences were noted

EFFECTS OF VARYING THE DISTANCE

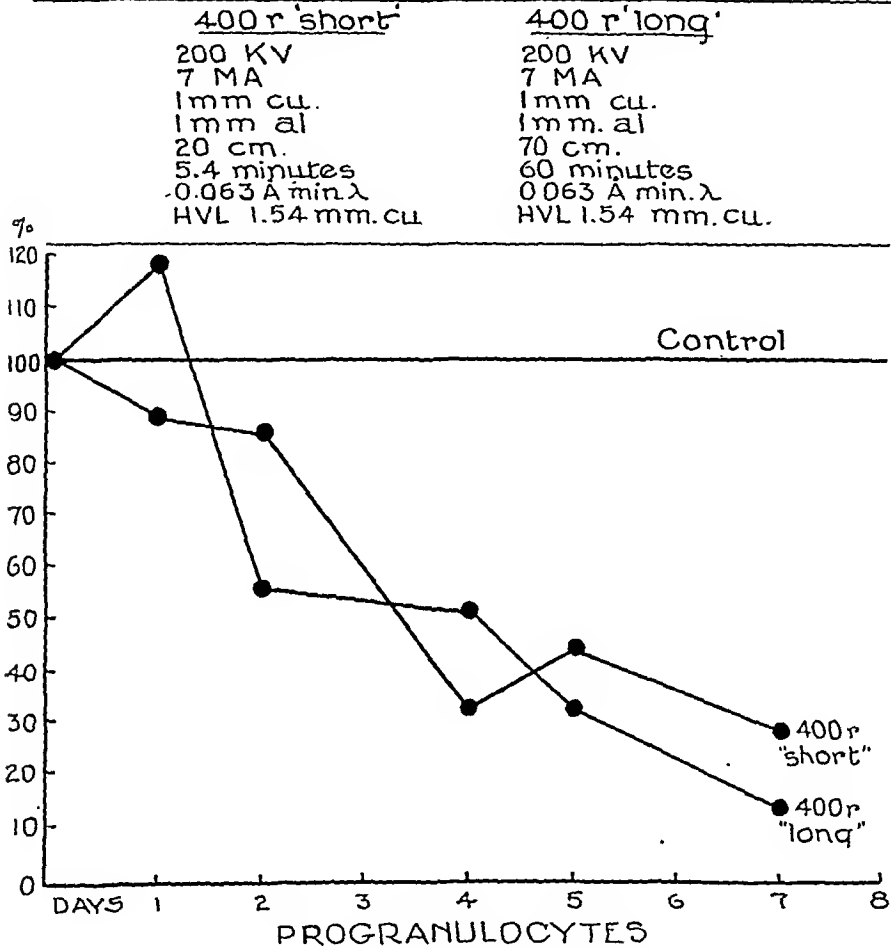


FIG. 5. Note that varying the time by varying the distance of the tube, keeping all other factors constant, did not significantly alter the effect. This was true for other doses and for the other cell types as well as for progranulocytes (promyelocytes).

in this experiment between the cells exposed to a dose of 400 r at the time of the first fractional dose and the divided exposures but much more work should be done before conclusions are justified.

THE EFFECT OF TRANSFERRING CULTURE MEDIUM FROM IRRADIATED VIALS TO NONIRRADIATED VIALS AND VICE VERSA

It is well known that in leukemias and sometimes Hodgkin's disease and lymphosarcoma, irradiation of one area may be followed by diminution in size of lymph nodes that were not irradiated. Some have thought that this might be explained by the production of some substance circulating in the

blood through which the action of roentgen-rays was mediated. To investigate this possibility, 2 controls were placed in the box side by side with two vials which were given identical doses of roentgen-rays. Immediately after irradiation in some studies and 20 hours after irradiation in others the vials were centrifugated and the supernatant fluid from one of the controls and one of the irradiated cultures was withdrawn and the fluid from the control placed in the vial containing irradiated cells and the fluid from the irradiated cultures placed in the vial containing nonirradiated cells. In the experiments in which this was done the irradiated cells with nonirradiated medium showed a curve of decrease similar to that for the culture with irradiated cells and medium; whereas, the nonirradiated cells with medium which had been irradiated showed no significant deviation from the control. These experiments would suggest that in the time after irradiation studied no humoral mechanism was involved in the action of irradiation but that this action was directly on the cells. Many more experiments with transfer of medium at different time intervals are obviously needed before a humoral action can be excluded.

THE EFFECTS ON MITOTIC AND AMITOTIC CELL DIVISION

Previous studies⁷ with the marrow culture method have shown that progranulocytes (promyelocytes), prolymphocytes, promonocytes and all of the blast cells undergo mitotic division; that the lymphocytes, plasmacytes and prokaryocytes (erythroblasts) undergo only amitotic division; and that the cells of the granulocyte series more mature than the progranulocyte (promyelocyte) do not divide. In the marrow cultures which have been used in these experiments, lymphocytes and progranulocytes (promyelocytes) are the only cells that divide which have been present in sufficient numbers to make counts practical. It was early observed that mitoses which were readily found in the control cultures were not seen in the irradiated cultures, but since less than 1 per cent of the cells in the controls were ordinarily in mitosis it was difficult to count enough cells to get statistically significant figures for the cells in mitosis. Since colchicine has been shown⁸ to stop mitosis in the metaphase it was used as an indicator of the effects on mitosis. Preliminary experiments indicated that some mitoses were affected* by concentrations of colchicine as low as 1-10,000,000 but that all mitoses were not affected by concentrations much less than 1-100,000. In those marrows which were studied with concentrations of 1-100,000 no mitoses were found not showing typical colchicine effects. It is not definitely known whether colchicine has other effects on the cells than stopping mitosis nor is it known for certain whether colchicine merely slows cell division resulting in ultimate reformation of a nucleus and maturation, or whether the cell eventually dies. It was observed, however, that the number of progranulocytes (promyelocytes) showing colchicine mitoses progres-

* See figure 1 in Osgood, E. E.: Culture of human marrow as an aid in evaluation of therapeutic agents: studies of sulfanilamide and related compounds, Jr. Lab. and Clin. Med., 1939, xxiv, 954.

sively increased for a period of time and then decreased, indicating that the cells must either disintegrate or that the nucleus must eventually reform and the cells mature.

In studying the effect of roentgen-rays on mitosis a control culture without colchicine or irradiation was studied, also a culture with 1–100,000 colchicine alone, a culture with 1–100,000 colchicine irradiated with a dose of 400 r, and a culture with 400 r irradiation alone. Experiments were done in which the colchicine was added 20 hours before irradiation and others in which the colchicine was added immediately after irradiation. In one of the experiments in which colchicine was added 20 hours before irradiation, the culture containing colchicine alone, studied 40 hours after addition of the colchicine, showed mitosis stopped in the metaphase in 57 of the 100 progranulocytes (promyelocytes) counted. At the same time in the culture containing colchicine, which was irradiated 20 hours before, no mitoses were found in counting 100 progranulocytes (promyelocytes) and only three were found in a half hour's search using an 8 mm. objective and a magnification of $200\times$ which permitted a survey of thousands of cells. By 68 hours after irradiation, two colchicine mitoses in about 3,000 cells could be found in the irradiated culture containing colchicine and mitoses were still numerous in the culture containing colchicine alone. Mitoses were still very scarce at four and five days in the irradiated culture which contained colchicine. This experiment would seem to show that roentgen-rays prevented the onset of mitosis since any mitoses occurring during this time should have been stopped by colchicine.

Lymphocytes in amitotic division were found in control cultures and seemed less numerous in irradiated cultures. However, no method of arresting amitotic division was available so statistically significant counts were not obtained. The decrease in lymphocytes gave such smooth, straight line curves without increase in disintegrating lymphocytes that a decreased production rather than increased destruction seems most probable.

COMPARISON OF THE EFFECTS OF ROENTGEN-RAYS AND COLCHICINE

Quantitative studies of each cell type were made in the studies on mitosis using colchicine as an indicator. Since colchicine held mitosis in the metaphase and some investigators have thought that the major effect of roentgen-rays occurs during mitosis, it seemed possible that the roentgen-rays and colchicine might have an additive effect. The results observed, however, were that colchicine had no effect on the lymphocytes, as would be expected, since lymphocytes have never been observed in mitotic division, and that the effect of colchicine alone on the cells of the granulocyte series was to give curves similar in character and slope to those obtained with roentgen-rays. Most interesting of all, the combination of roentgen-rays and colchicine showed no additive effect on the cells of the granulocyte series, the curves agreeing within the limits of experimental error with the curves for the culture containing colchicine alone and also for the culture receiving 400 r

of roentgen-rays alone. On the other hand, the lymphocytes in the culture receiving both roentgen-rays and colchicine showed a curve corresponding to the culture receiving roentgen-rays alone and not to that containing colchicine alone. Unfortunately, only a few experiments were completed using colchicine as indicator and the concentration of 1–100,000 is above the concentration which is fatal to human beings and animals. More work is in progress on the comparative effects of colchicine, roentgen-rays and combinations of the two since this line of investigation seems to offer great promise.

THE EFFECT OF IRRADIATION ON THE MORPHOLOGY OF THE CELLS

The majority of the cells in the irradiated cultures were similar in morphology, motility, and phagocytic ability to the corresponding cells in the control nonirradiated cultures. However, a few cells with giant bizarre shaped nuclei were noted in the cultures receiving irradiation. These changes in the nucleus were first noticed in the progranulocytes (promyelocytes) and from day to day the cells showing alterations would be more mature, next appearing as granulocytes (myelocytes), then metagranulocytes (metamyelocytes), rhabdocytes (staff cells), and finally as lobocytes (polymorphonuclears). The structure of the nucleus was similar to that described by O. P. Jones⁹ for the cells of the granulocyte series in the sternal marrow of patients with pernicious anemia. A few such cells were found in the control cultures, also, and they are occasionally found in other cultures. It seems possible that these cells may represent polymers or other chromosomal aberrations and that roentgen-rays increase the number of mutant cells over those which naturally occur. Our data, however, are not sufficient to prove this.

COMPARISON OF THE EFFECTS OF IRRADIATION ON LEUKEMIC AND NONLEUKEMIC CELLS

Studies of the effects of irradiation on marrow or blood cultures from four cases of chronic granulocytic (myelogenous) leukemia and three cases of lymphocytic leukemia have been compared with cultures of nonleukemic cells. The curve for each type of cell fell within the limits of variation noted for the same irradiation on the corresponding nonleukemic cell, except in one patient with chronic granulocytic (myelogenous) leukemia who had received a total of 700 r of irradiation to the chest and 300 r to the spleen, given every two days in doses of 100 r, the last treatment being two days before marrow was obtained for culture. In this patient there was distinctly less effect than for a similar dose of roentgen-rays on nonleukemic cells of the same type. Since in this type of experiment different marrow cultures have to be compared, the control is not as adequate as in the other experiments and a much larger series must be studied before it can be concluded that there is no difference in the type of effect on leukemic and nonleukemic cells.

COMMENT

Any theory of the action of roentgen-rays on these marrow cultures must explain the gradual decrease in cell count without a corresponding increase in disintegrating cells. It must explain the latent period before the effects become manifest on the more mature cells of the granulocyte series. It must explain the fact that the lobocytes (polymorphonuclears) are not killed in a period of four days by even such large doses as 2,000 r, and the fact that a few of the most sensitive cells, such as the lymphocytes and progranulocytes (promyelocytes) may still be found several days after large doses have been given although most of the cells have disappeared before this. It must explain the absence of mitotic figures even when colchicine is used as an indicator and the fact that the effects of colchicine on cells of the granulocyte series are similar to the effect of roentgen-rays but are not similar on lymphocytes which undergo only amitotic division.

It can be shown mathematically that if the action of roentgen-rays were to prevent the occurrence of either mitotic or amitotic division in the cells and if only the progranulocytes (promyelocytes) among cells of the granulocyte series were capable of division that curves of this general shape would result and there would be no increase in the rate of cell death but only a decrease in the rate of cell multiplication. The effects might be compared to those which would occur in a population group of human beings if reproduction occurred only in newborn infants and all or many of the newborn infants were sterilized. A decrease in the number of newborn would first be noted as they matured to childhood; then the number of children would decrease as they matured to adolescence, and so on. The natural death rate of a particular group would not be altered, so that deaths would not increase in number in proportion to the number of the population alive at any age period, and the total number of deaths in a given time period would not increase although the population would eventually decrease.

The theory that roentgen-rays act only on cells in the process of division seems improbable since the number of cells affected is far greater than the number of cells found in the process of division at any one time. It is possible, however, that there is a certain time period in the intervals between division when cells are more sensitive than at other time periods. If this were the case, the same dose of roentgen-rays given over a period of the entire cycle from one division to the next for the cell type would be expected to have a greater effect than the same dose given in a short period of time. Judging from the number of cells in mitosis and the probable duration of mitosis in human cells, the duration of the cycle between cell division in these cells is probably of the order of 24 to 100 hours and if this were the case, differences would hardly be expected from variations in the time of exposure of only 5 minutes to 1 hour, but a difference with times of exposures such as are usually used in radium therapy would be expected. Work is in progress to investigate this possibility.

These experiments do not exclude a hastening of maturation as suggested by Isaacs.¹⁰ However, the increased proportion of more mature cells could be explained by a simple decrease in cell division among the immature cells with resultant aging of the cell population.

SUMMARY

The marrow culture method makes possible quantitative studies of the effects of irradiation on living human cells of different radio-sensitivity and stages of maturity. This preliminary study of several of the possible variables in roentgen-ray therapy indicates that this method should give information of value and suggests that irradiation in the doses employed in clinical roentgen therapy does not directly kill cells but does inhibit multiplication resulting in a gradual decrease in the cell populations as they mature and die. Colchicine should prove a valuable indicator of the effects of irradiation on mitotic division. Irradiation apparently inhibits amitotic division as well as mitotic division. Much work remains to be done with the method before final conclusions are warranted.

REFERENCES

1. DUGGAR, B. M.: Biological effects of radiation: mechanisms and measurement of radiation, applications in biology, photochemical reactions, effects of radiant energy on organisms and organic products, Vols. I and II, 1936, McGraw-Hill Book Co., New York.
2. SCOTT, C. M.: Some quantitative aspects of the biological action of X and γ rays, His Majesty's Stationery Office, London, 1937.
3. SELLING, L., and OSGOOD, E. E.: Action of benzol, roentgen rays, and radioactive substances on the blood and blood-forming tissues, Downey's Handbook of Hematology, 1938, iv, Pp. 2691-2801, Paul B. Hoeber, Inc., New York.
4. OSGOOD, E. E., and BROWNLEE, INEZ E.: Culture of human marrow: details of a simple method, Jr. Am. Med. Assoc., 1937, xviii, 1793.
5. YOUNG, R. H., and OSGOOD, E. E.: Sternal marrow aspirated during life: cytology in health and in disease, Arch. Int. Med., 1935, lv, 186.
OSGOOD, E. E., and ASHWORTH, CLARICE M.: Atlas of hematology, 1937, pp. 205-206, J. W. Stacey, Inc., San Francisco.
6. OSGOOD, E. E.: Culture of human marrow: length of life of the neutrophils, eosinophils and basophils of normal blood as determined by comparative cultures of blood and sternal marrow from healthy persons, Jr. Am. Med. Assoc., 1937, cix, 933.
7. OSGOOD, E. E.: The histogenesis, classification and identification of the cells of the blood and marrow based on cultures and hematologic studies of human marrow and blood, Am. Jr. Clin. Path., 1938, viii, 59.
OSGOOD, E. E., and ASHWORTH, CLARICE M.: Atlas of hematology, 1937, pp. 28-29, J. W. Stacey, Inc., San Francisco.
8. BRUES, A. M., and JACKSON, ELIZABETH B.: Nuclear abnormalities resulting from inhibition of mitosis by colchicine and other substances, Am. Jr. Cancer, 1937, xxx, 504.
9. JONES, O. P.: Origin of neutrophils in pernicious anemia (Cooke's macropolycytes): biopsies of bone marrow, Arch. Int. Med., 1937, lx, 1002.
10. ISAACS, R.: Maturing effect of roentgen rays on blood-forming cells, Arch. Int. Med., 1932, l, 836.

SULFANILAMIDE AND MENINGITIS *

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THE therapy of infections has developed almost exclusively along the lines of specificity, and an excellent example of this is the use of the many types of anti-serum for the treatment of pneumococcus pneumonia. Likewise in drug therapy, the real successes have been mostly specific in their application. Used at first as a specific in beta hemolytic streptococcus infections, the therapeutic trial of sulfanilamide and its derivatives has been extended clinically and experimentally to cover the most remarkable variety of infections. This list includes such dissimilar organisms as gram positive and negative micrococci, aerobic and anaerobic bacilli, acid fast bacilli, spirochetes, protozoa and even filterable viruses. Such reputed panaceal properties are beyond the realm of specificity, and experimental investigations do not speak for bacterial specificity but rather indicate a bacteriostatic^{1, 2} or indirect bactericidal³ effect against microorganisms widely diverse biologically. This mode of action suggests a new approach in therapy. The actual practical value of this bacteriostatic or bactericidal effect has yet to be defined in clinical terms. Meanwhile careful experimental and clinical studies will probably tend to reduce the exaggerated expectations as to the therapeutic possibilities of the drug as well as establish its proper status.

In experimental work, the survival or death of the animal is the criterion of the success or failure of the therapeutic experiment. It occurred to us that analogous conditions are available clinically in a disease like meningitis. Meningitis, produced by the streptococcus, pneumococcus, staphylococcus, influenza bacillus and tubercle bacillus as well as some rare organisms, is almost invariably fatal, regardless of the treatment. Tripoli's⁴ mortality rate for 247 cases of meningitis due to other organisms than the meningococcus was 98.3 per cent. Meningitis, due to any of these organisms, should therefore offer an excellent testing ground for the therapeutic worth of sulfanilamide, as recovery in such a disease may almost unquestionably be ascribed to the drug. Meningococcus meningitis also, with or without specific serum treatment, has such a mortality that a substantial reduction in the death rate under sulfanilamide therapy should be significant.

The following 22 cases of meningitis are offered as illustrations of the

* Received for publication June 25, 1938.

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We wish to thank the Staffs of Hahnemann, St. Luke's and West Jersey Hospital for permitting us to treat these cases.

The sulfanilamide used was kindly furnished by the Abbott Laboratories and the Winthrop Chemical Co.

therapeutic value and action of sulfanilamide. They are discussed, along with sulfanilamide treated meningitis cases found in the literature, under the various types of infection. Our cases were treated practically exclusively with sulfanilamide, given either orally, subcutaneously or intrathecally.

Hemolytic Streptococcus Meningitis. It is safe to say that in the past a patient with streptococcic meningitis was regarded as an almost certain fatality. It is true occasional cases recovered, but these were so rare that the literature of recovery is one of single case reports, in which the outcome is ascribed to most varied methods of treatment. Gray,⁵ in his comprehensive review, estimated the mortality at over 97 per cent. Long and Bliss⁶ say the fatality rate in hemolytic streptococcus meningitis is about 99 per cent. Canfield's⁷ mortality was 97 per cent, Zeligs'⁸ 98 per cent and Tripoli's⁴ 91.6 per cent. In the 37 available cases at Johns Hopkins Hospital⁹ in the last 15 years, there was not a single recovery. Neal and Applebaum¹⁰ state that among 274 cases of various types of streptococcus meningitis, there was a death rate of 94.5 per cent.

Under sulfanilamide, there tends to be almost a reversal of these figures and, as Neal and Applebaum¹⁰ remark, the results seem quite astounding. Whether the credit is due entirely to sulfanilamide or whether the present strains of streptococcus are less virulent or whether these results will continue remains to be seen. Of 28 cases of hemolytic streptococcus meningitis of which Long and Bliss⁶ have knowledge, 85 per cent recovered under the drug. Applebaum¹¹ reports 26 cases of otitic or sinus origin with a recovery rate of 80.7 per cent. Trachsler¹² had four recoveries out of seven, but one of the fatal cases was due to a *Streptococcus viridans*. Carey¹³ had four cases of hemolytic streptococcus meningitis treated with sulfanilamide, all of which recovered. Arnold had six cases, all recoveries, but these are probably included in Long and Bliss's⁶ list. Some of the foregoing cases received also antimeningococcus or antistreptococcus serum or some adjuvant treatment such as transfusions, but these methods produced almost no recoveries before and it is questionable whether they act synergistically with sulfanilamide. Single case reports have the disadvantage of recording, as a rule, only successes. It is important to report failures with this treatment as well as successes to get an accurate estimate of its value.

Our own six cases of hemolytic streptococcus meningitis (table 1) received sulfanilamide only and no serum, although some were transfused when convalescent. Our figures for recovery are lower than others, four out of six or 67 per cent. The results are still in striking contrast with the presulfanilamide era. Of the 70 cases cited here, including our own, 57 or 81.4 per cent recovered.

Streptococcus viridans Meningitis. Meningitis due to *Streptococcus viridans* is much less common than that due to the beta hemolytic strep-

TABLE I
Streptococcus Hemolyticus Meningitis

Case	Date	Symptoms		Spinal Fluid		Treatment
		Status of Patient	Temperature	Appearance Cell Count	Bacteriology	
No. 1— S. M. 16 yrs. male	6- 5-37 2nd day of disease	Nuchal rigidity. Lethargic	102°	Opalescent 330 cells mostly polys	Hemolytic streptococcus	0.8% Sulfanilamide 30 c.c. intrathecally 170 c.c. subcutaneously 30 c.c. intrathecally 170 c.c. subcutaneously
	6- 6-37	Same	102.2°	Same	Sterile	Same
	6- 7-37	Generally better	99.6°	Same	Sterile	30 c.c. intrathecally 100 c.c. subcutaneously
	6- 8-37	Improved	99.0°	Same		20 c.c. intrathecally 150 c.c. subcutaneously
	6- 9-37		98.6°	450 cells	Sterile	Sulfanilamide 15 grains every 6 hours
	6-27-37	Discharged				No medication since 6-12-37
No. 2— H. K. 7 yrs. male	6-30-37 3rd day of disease	Headache, photophobia. Positive Kernig	105.8°	Cloudy, 6,800 cells	Hemolytic streptococcus	0.8% Sulfanilamide 10 c.c. intrathecally 115 c.c. subcutaneously
	7- 1-37	Mastoidectomy, 6-30	103.8°	Cloudy	Sterile	10 c.c. intrathecally 115 c.c. subcutaneously 10 c.c. intrathecally 115 c.c. subcutaneously
	7- 2-37		102.0°	Cloudy		Same
	7- 3-37	Slightly better	101.0°	Cloudy	Sterile	10 c.c. intrathecally 115 c.c. subcutaneously
	7- 4-37		101.4°			Same
	7- 5-37	Improved	100.0°	Opalescent		Same, plus blood trans- fusion, 200 c.c.
	7- 6-37	Improved	98.8°			125 c.c. subcutaneously
	7-26-37	Discharged. Wound still healing	98.8°			30 grains daily from 7-7 to 7-15. No further med- ication
No. 3— J. S. W.	12-21-37 2nd day of disease	Stuporous. Nuchal rigidity	104.6°	Purulent	Hemolytic streptococcus	0.8% Sulfanilamide 15 c.c. intrathecally 110 c.c. subcutaneously 30 grains orally
	12-22-37		105.6°			60 grains orally
	12-23-37	Died 29 hrs. after admission and 48 hrs. after onset of meningitic symptoms. Autopsy—Right mastoiditis. Purulent meningitis				

TABLE I (Continued)

Case	Date	Symptoms		Spinal Fluid		Treatment
		Status of Patient	Temperature	Appearance Cell Count	Bacteriology	
No. 4— E. S. 6 yrs. female	2-20-38 2nd day of disease	Semi-conscious	105.4°			
	2-21-38	Nuchal rigidity	105.0°			
	2-22-38	Positive Kernig. Otitis media	103.0°	Slightly cloudy 608 cells	Hemolytic streptococcus	60 grains sulfanilamide
	2-24-38		103.0°	1500 cells	Hemolytic streptococcus	30 grains sulfanilamide
	2-29-38	Slight improvement	103.8°	300 cells		30 grains daily since 2-24-38
	3- 4-38		101.0°	Purulent. 1 c.c. obtained	Hemolytic streptococcus	Same
	3-12-38	Condition same	100.0°	Same	Same	0.8% Sulfanilamide 8 c.c. intrathecally 115 c.c. subcutaneously
	3-13-38		100.0°			8 c.c. intraspinally 115 c.c. subcutaneously
	3-16-38	Comatose hemiplegia	102.4°			Blood transfusion 150 c.c.
Died	3-21-38	Died	107.0°			
No. 5— J. L. 8 yrs. male	3-10-38 4th day of disease 3-10-38	Delirious. Nuchal rigidity. Photophobia. Mastoidectomy	102°	682 cells	Hemolytic streptococcus	0.8% Sulfanilamide 10 c.c. intrathecally 30 grains orally
	3-11-38		105°	700 cells	Sterile	10 c.c. intrathecally 260 c.c. subcutaneously 25 grains orally
	3-12-38	Improved	103°	540 cells		6 c.c. intrathecally 125 c.c. subcutaneously Blood transfusion 250 c.c.
	3-13-38		102°			10 c.c. intrathecally 120 c.c. subcutaneously 15 grains orally
	3-15-38	Feels better		680 cells	Hemolytic streptococcus	9 c.c. intrathecally 25 grains daily, orally
	3-18-38	Greatly improved	99°	380 cells	Sterile	20 grains orally daily
	3-22-38		98.6°			15 grains daily since 3-19-38
	4- 6-38	Mastoid wound healing. Discharged				
Recovered						

TABLE I (Continued)

Case	Date	Symptoms		Spinal Fluid		Treatment
		Status of Patient	Temperature	Appearance Cell Count	Bacteriology	
No. 6— A. A. 12 yrs. female	5- 2-38	Delirious. Photophobia. Marked nuchal rigidity, positive Kernig	103.4°	7500 cells	Hemolytic streptococcus	0.8% Sulfanilamide 12 c.c. intrathecally 113 c.c. subcutaneously 18 c.c. intrathecally 107 c.c. subcutaneously 15 grains orally
	5- 3-38	More rational	102.6°	5000 cells	Sterile	10 c.c. intrathecally 8 c.c. intrathecally 115 c.c. subcutaneously 30 grains orally
	5- 4-38	Clinically improved. Rigidity. Positive Kernig still present	101.0°	6400 cells	Sterile	10 c.c. intrathecally 35 c.c. subcutaneously 30 grains orally
	5- 5-38	Generally better	100.6°	1400 cells	Sterile	10 c.c. intrathecally 105 c.c. subcutaneously 30 grains Blood transfusion 250 c.c.
	5- 6-38	Continues to improve	100.2°			40 grains orally
	5- 7-38	Better	100.0°			40 grains orally
	5- 8-38	Generally better	100.8°			40 grains orally
	5- 9-38	Rigidity slight but generally better	99.0°			30 grains orally
	5-10-38	No complaint	99.0°			30 grains orally
	5-11-38	No complaint	98.6°			20 grains orally
	5-12-38	No complaint, apparently recovered. Kept for further observation	98.6°			
Recovered						

tococcus. In Neal, Jackson and Applebaum's¹⁴ series of 205 cases of streptococcus meningitis, the hemolytic types were about 10 times as numerous as the non-hemolytic forms. Applebaum¹¹ has three cases of non-hemolytic streptococcus meningitis of otitic origin treated by sulfanilamide. One case recovered. Trachsler's¹² one case died in spite of sulfanilamide but there was a possible complication of basal fracture. We treated two cases (table 2). One case was in a desperate condition when seen and, although treated intensively with sulfanilamide, survived only 15 hours after admission to the hospital. The other case responded to the drug treatment satisfactorily, but the organism isolated was difficult to place. Morphologically, it resembled a pneumococcus more than a streptococcus but failed to type with any of the 32 antisera. This result was confirmed at two other laboratories. The organism was not bile soluble, produced a green zone on human, rabbit and horse blood agar plates and we finally concluded it was a *Streptococcus viridans*. This gives two recoveries out of six cases, a mortality of 67 per cent.

Mellon and Cooper,¹⁵ in discussing the biphasic nature of certain Group A hemolytic streptococci, speak of the possibility of sulfanilamide being misinterpreted as curing *Streptococcus viridans* infections which are really caused by hemolytic streptococci stabilized in a viridans phase. This might apply to some of the cases reported.

TABLE II
Streptococcus viridans Meningitis

Case	Date	Symptoms		Spinal Fluid		Treatment
		Status of Patient	Temperature	Appearance Cell Count	Bacteriology	
No. 1— R. P. 5 yrs. male	10-22-37 2nd day of disease	Moderate nuchal rigidity. Positive Kernig. Nasopharyngitis	102.6°	576 cells	<i>Streptococcus viridans</i>	55 grains sulfanilamide orally
	10-23-37	Photophobia	102.4°	Slightly cloudy	Same	0.8% Sulfanilamide 7 c.c. intrathecally 115 c.c. subcutaneously 7 c.c. intrathecally 110 c.c. subcutaneously
	10-24-37	Rigidity less marked	101.8°	Slightly cloudy	Sterile	55 grains orally
	10-25-37	Generally better	99.8°			30 grains orally
	10-26-37	Improving	99.4°			35 grains orally
	10-27-37	Practically well	99.4°			No medication
	11- 3-37	No complaints	98.8°	10 cells		No medication
	11- 7-37	Discharged				
Recovered						
No. 2— M. P. 59 yrs. male	4- 3-38 3rd day of disease	Headache Vomiting				0.8% Sulfanilamide
	4- 4-38	Restless Toxic Confused Myringotomy. Moderate nuchal rigidity	100.0° 102.6° 105.2°	Cloudy 3900 cells	<i>Streptococcus viridans</i>	25 c.c. intrathecally 25 c.c. intravenously 75 c.c. subcutaneously 25 c.c. intrathecally 100 c.c. subcutaneously 100 c.c. intravenously 100 c.c. intravenously 100 c.c. intravenously
	4- 5-38	Delirious Extremely restless. Died 36 hrs. after admission	104.2°			100 c.c. intravenously 100 c.c. intravenously
Died						

Pneumococcic Meningitis. Pneumococcic meningitis is slightly more common than streptococcic meningitis¹⁴ but certainly there have been fewer attempts to treat it with sulfanilamide than the streptococcic form. Its high fatality may be judged by Tripoli's⁴ paper in which he reports 111 cases with but one recovery. Mertins and Mertins¹⁶ in surveying the literature of the past 15 years found only 31 cases in which recovery followed various procedures advocated by the respective authors. These authors

report a case of recovery following sulfanilamide therapy: the actual type was not determined although marked Type 4. Caldwell and Byrne¹⁷ cite a Type 1 case successfully treated with the drug. The typing was done by the precipitin and not by the Neufeld capsule method, as cultures were sterile. Mitchell and Trachsler¹⁸ report a case of Type 5 pneumococcic meningitis recovering after the use of optochin and sulfanilamide. They are inclined to give the credit to the optochin. Basman and Perley¹⁹ report three cases treated with sulfanilamide. Two, one a Type 3, the other untyped, died. The third, a Type 5, recovered. Applebaum¹¹ reports 32 cases treated with the drug, of which four recovered. The predominating types were 1 and 3. We had one case, a Type 27, with complete recovery after sulfanilamide (table 3). None of the recovered cases received anti-pneumococcus serum;

TABLE III
Pneumococcus Meningitis

Case	Date	Symptoms		Spinal Fluid		Treatment
		Status of Patient	Temperature	Appearance Cell Count	Bacteriology	
No. 1— E. B. 11 yrs. male	8-17-37 3rd? day of disease	Headache, vomiting, lateral nystagmus	103.0°	Cloudy	Pneumococcus Type 27	0.8% Sulfanilamide 15 c.c. intrathecally 230 c.c. subcutaneously 15 c.c. intrathecally 110 c.c. subcutaneously
	8-18-37	Same	104.0°	Cloudy		11 c.c. intrathecally 110 c.c. subcutaneously 15 c.c. intrathecally 110 c.c. subcutaneously
	8-19-37	Clinically better	101.4°	Opalescent 380 cells		14 c.c. intrathecally 75 grains orally
	8-23-37	Improving	97.4°	65 cells	Sterile	9 c.c. intrathecally
	8-29-37	Drowsy	100.2°	26 cells		60 grains orally since 8-27-37
	9- 5-37	Fully recovered				

some received a few preliminary doses of antimeningococcic serum. There were three examples of meningitis due to Type 3 pneumococcus. All of these died in spite of the fact that Type 3 infection other than meningeal has reacted rather encouragingly to sulfanilamide. The total number of cases treated with sulfanilamide is 39 of which 30 or 76 per cent died, a high mortality but less than without it.

Influenzal Meningitis. Fothergill²⁰ found the mortality in untreated cases of influenzal meningitis about 98 per cent. Among 201 serum-treated cases, including series of Silverthorne, Fraser and Snelling²¹ and Schwentker,²² the mortality was 84.6 per cent. Silverthorne, Fraser and Snelling²¹ also report a mortality of 98 per cent in 70 untreated cases but the mortality in 36 serum-treated cases was only 72 per cent.

Of 18 cases of influenzal meningitis treated by sulfanilamide, Apple-

baum¹¹ reports but one recovery. We found five other cases in the literature,^{23, 24, 25, 19} all of which died. Both of our cases (table 4) succumbed. The one recovery received both anti-influenzal serum and sulfanilamide (prontosil and sulfanilamide), and Neal¹⁰ emphasizes this point, citing Provitzky's experiments on mice in which a combination of serum and sulfanilamide had a curative effect in otherwise fatal inoculations. Three other cases received both serum and sulfanilamide but ended fatally. The

TABLE IV
Influenzal Meningitis

Case	Date	Symptoms		Spinal Fluid		Treatment
		Status of Patient	Temperature	Appearance Cell Count	Bacteriology	
No. 1— S. T. 11 mon. female	12-14-37 6th? day of disease	Marked nuchal rigidity, listless, hydrocephalus	103.2°	1600 cells	<i>H. influenzae</i>	0.8% Sulfanilamide
	12-15-37	Strabismus, more listless	103.2°	Purulent	<i>H. influenzae</i>	125 c.c. subcutaneously 175 c.c. subcutaneously
	12-16-37	Cephalic ery	103.0°	1000 cells 90 c.c. ventricular	<i>H. influenzae</i>	20 c.c. intraventricularly 10 c.c. intrathecally 125 c.c. subcutaneously 95 c.c. subcutaneously
	12-18-37		104.0°	50 c.c. ventricular 400 cells	<i>H. influenzae</i>	20 c.c. ventricularly 10 c.c. intrathecally 90 c.c. subcutaneously
	12-19-37	Stuporous	103.4°	200 cells	<i>H. influenzae</i>	15 c.c. intraventricularly 10 c.c. intracisternally 5 c.c. thoracic spine 5 c.c. lumbar spine
	12-20-37	Died Autopsy—Purulent meningitis. Internal hydrocephalus.				
No. 2— B. J. F. 3 mon. female	2-22-38 5th? day of disease	Listless, moderate nuchal rigidity	104.6°	Purulent	<i>H. influenzae</i>	10 c.c. 2.5% Prontosil subcutaneously
	2-23-38	Twitching of muscles	104.4°	Purulent	<i>H. influenzae</i>	0.8% Sulfanilamide 15 c.c. intrathecally 110 c.c. subcutaneously 20 c.c. Prontosil subcutaneously
	2-24-38	Marked nuchal rigidity	104.4°	Purulent	<i>H. influenzae</i>	15 c.c. intrathecally 110 c.c. subcutaneously 125 c.c. subcutaneously
	2-25-38	Condition unchanged	104.0°	Purulent	<i>H. influenzae</i>	15 c.c. intrathecally 110 c.c. subcutaneously 15 c.c. intrathecally 110 c.c. subcutaneously
	2-26-38		104.6°	Cloudy		10 c.c. intrathecally 115 c.c. subcutaneously
	2-27-38	Cyanotic at times	104.0°	Cloudy		20 c.c. intracisternally 105 c.c. subcutaneously
	2-28-38	Condition critical	104.6°			
	3- 1-38		101.0°			
	3- 2-38	Died				

results with sulfanilamide therapy in influenzal meningitis with or without serum so far, therefore, are not encouraging, there being 24 deaths in 25 cases, a mortality of 96 per cent. This is in contrast to the purely serum treated cases cited above.

Tuberculous Meningitis. The case of tuberculous meningitis herewith (table 5) reported was brought to the hospital in a critical condition and

TABLE V
Tuberculous Meningitis

Case	Date	Symptoms		Spinal Fluid		Treatment
		Status of Patient	Temperature	Appearance Cell Count	Bacteriology	
No. 1— C. H. 19 mon. male	3-1-38 8th? day of disease	Stuporous. Moderate nuchal rigidity. Positive Kernig	101.0°	Opalescent 375 cells lymphocytic	Direct smear negative. Culture on ordinary media sterile	20 c.c. 2.5% Prontosil intramuscularly.
	3-2-38	Marked rigidity	102.0°	Opalescent	Sterile	0.8% Sulfanilamide 10 c.c. intrathecally 235 c.c. subcutaneously
	3-3-38	Condition grave. Died	104.6°			125 c.c. subcutaneously
		Autopsy report: Tuberculous meningitis. Mediastinal lymph node and pulmonary tuberculosis			4-2 tubercle bacillus on Petrognani medium (Cowan and Henderson modification)	
Died						

survived only 48 hours, during which time she was treated with intrathecal and subcutaneous doses of protosil and sulfanilamide. A pure culture of the tubercle bacillus was obtained from the spinal fluid on Petrognani medium and the necropsy revealed tuberculous meningitis as well as pulmonary and lymph node involvement. We were unable to find in the literature any case treated with the drug. Rich and Follis,²⁶ however, in experimental tuberculosis in the guinea pig found that sulfanilamide exerted a striking inhibitory effect upon the development of lesions as compared with controls.

Meningitis of Undetermined Origin. The first of these two cases (table 6) in which we were unable to demonstrate the causal organisms was an adult whose history suggested a streptococcus infection following a tonsil operation. He was critically ill with meningitis when admitted to the St. Luke's hospital and lived but four days, during which time his spinal fluid was densely cloudy with very numerous polynuclears but no demonstrable bacteria, although the fluid was examined carefully and cultured daily on various media. The second case was a mild type in a child and lymphocytic choriomeningitis was considered, but the polynuclears were definitely predominant on all occasions. Here repeated spread examinations

and cultures were all negative. Cultures for tubercle bacilli and guinea pig inoculations were also negative. Recovery was complete and uncomplicated.

Cases like these are not very uncommon. Tripoli⁴ among 468 patients had 26 or 5 per cent of cases of purulent meningitis in which the type of organism was not reported. One of Schwentker's²⁷ cases of meningitis

TABLE VI
Undetermined Meningitis

Case	Date	Symptoms		Spinal Fluid		Treatment
		Status of Patient	Temperature	Appearance Cell Count	Bacteriology	
No. 1— A. P. F. 30 yrs. male	7-10-37 4th day of disease	Stuporous severe headache	103.0°	Purulent	Smear and culture negative	0.8% Sulfanilamide 20 c.c. intrathecally 355 c.c. subcutaneously
	7-11-37	Marked nuchal rigidity	104.0°	Purulent	Smear	250 c.c. subcutaneously 55 c.c. intrathecally 250 c.c. subcutaneously
	7-12-37	Condition grave	108.0°	Cloudy yellow, 10,000 cells polynuclears	Smears and cultures nega- tive. Anaer- obic cultures not made	35 c.c. intrathecally 30 c.c. intrathecally 150 c.c. subcutaneously Blood transfusion 400 c.c.
	7-13-37	Died				
No. 2— T. W. 10 yrs. male	12- 1-37	Nuchal rigid- ity. Positive Kernig	104.0°	Opalescent 104 cells	Sterile	0.8% Sulfanilamide
	12-14-37	Photophobia. Blood culture sterile	104.8°			30 grains orally
	12-15-37	Restless, con- dition poor	104.0°	465 cells 75% polynuclears	Smear and culture nega- tive. Guinea pig inocula- tion negative (2-2-38)	10 c.c. intrathecally 115 c.c. subcutaneously 15 c.c. intrathecally 110 c.c. subcutaneously 15 grains orally
	12-16-37	Delirious	103.2°		Sterile	Same as 12-15
	12-17-37	Somewhat improved	100.2°	70 cells	Sterile for tu- bercle bacillus 3 weeks later on Petrognani medium. Cowen and Henderson modification	20 c.c. intrathecally 105 c.c. subcutaneously 15 grains orally
	12-18-37	Less irritable	102.0°			10 c.c. intrathecally 115 c.c. subcutaneously 10 c.c. intrathecally 115 c.c. subcutaneously 15 grains orally
	12-22-37	Improved	100.4°	60 cells	Sterile	From 12-19 to 12-22, re- ceived one-half the dose of 12-18
	12-26-37	Rigidity absent	99.4°			No medication
	12-30-37	Mantoux test (1 : 100) negative	99.4°			
	1- 7-38	Clinically negative	98.8°			
	1-14-38	Discharged				
Recovered						

was diagnosed meningococcic on a clinical basis, the organism not being demonstrable. We had a case of densely purulent meningitis following immediately upon a pneumonia and clinically pneumococcic meningitis. The most careful bacteriological examinations failed to reveal any bacteria.

Of several possible explanations, one is that, in the sulfanilamide cases, the organisms were missed in the primary examination and that later the sulfanilamide had sterilized the fluid. Another, perhaps more likely, is that the organisms were anaerobic. McDonald,²⁸ in discussing the rôle of anaerobic streptococci in human infections, cites four cases of meningitis in which anaerobic streptococci were isolated from the meninges at autopsy. F. W. Smith²⁹ recently reported a case of meningitis successfully treated with sulfanilamide, in which an anaerobic beta hemolytic streptococcus was isolated. This organism failed repeatedly to grow aerobically. We did not make definite anaerobic cultures in our cases and may have missed the causative organism this way. Smith's case, however, showed micrococci in the spread, whereas ours showed none at any time.

Meningococcus Meningitis. The mortality for meningococcus meningitis of course varies for different years and different locations. The United States Public Health Reports³⁰ for 1934 and 1935 list 6650 cases with a fatality of 53.2 per cent. Presumably most of these and likewise the cases which follow were serum treated. Tripoli⁴ found the mortality in the New Orleans Charity Hospital for the period 1925-1934 was 65.15 per cent. The Memphis³¹ fatality rate for 537 cases in the period 1925-1933 was 52.1 per cent. Levy³¹ in 176 patients treated with meningococcus antitoxin had a mortality of 34.6 per cent. In 135 of his patients ranging in age from one to 30 years, the mortality was 23.8 per cent. Hoyne³² reported 96 patients serum treated exclusively by the intravenous route with a mortality of 15.9 per cent.

Of cases treated with sulfanilamide, Schwentker³³ reports 52 patients with a mortality of 15.4 per cent. He compares these results with those attained in 278 consecutive patients treated with antimeningococcus serum in the same institution in the months immediately preceding the introduction of sulfanilamide therapy. In these the mortality was 30 per cent. In 24 other cases^{23, 18, 34, 19, 35, 36, 10, 37} there was only one death, a mortality of 4.2 per cent. Our own cases amount to eight and of these two died, a mortality of 25 per cent. The total is 84 cases with 11 deaths, a mortality of 13 per cent. A number of these cases received both serum and sulfanilamide, which clouds the issue as to the merit of sulfanilamide alone. Carey's³⁵ results are rather noteworthy. His five patients received sulfanilamide and no serum and all recovered, and furthermore only one received sulfanilamide intrathecally. Three had blood stream infections and two of these were given sulfanilamide intravenously with apparently good results.

TABLE VII
Meningococcic Meningitis

Case	Date	Symptoms		Spinal Fluid		Treatment
		Status of Patient	Temperature	Appearance Cell Count	Bacteriology	
No. 1— R. V. 10 yrs. male	6- 4-37 4th day of disease	Delirious. Nuchal rigidity. Photophobia	102.4°	Cloudy	Meningococcus	0.8% Sulfanilamide 15 c.c. intrathecally 110 c.c. subcutaneously
	6- 5-37	Rational	99.8°	Cloudy	Meningococcus	10 c.c. intrathecally 115 c.c. subcutaneously 20 c.c. intrathecally 105 c.c. subcutaneously
	6- 6-37	Nuchal rigidity marked	102.4°	Cloudy	Sterile	20 c.c. intrathecally 105 c.c. subcutaneously
	6- 7-37		102.2°	Cloudy	Sterile	10 c.c. intrathecally 90 c.c. subcutaneously
	6- 8-37	Improved	101.6°	Opalescent		8 c.c. intrathecally 70 c.c. subcutaneously
	6-14-37	Greatly improved	99.4°			80 c.c. subcutaneously on 6-9. 100 c.c. on 6-10. 25 grains daily since 6-11
Recovered	6-19-37	Discharged				
No. 2— D. N. 15 yrs. female	6- 2-37 2nd day of disease	Unconscious. Nuchal rigidity	102.6°	Cloudy 19,900 cells	Meningococcus	0.8% Sulfanilamide 30 c.c. intrathecally 300 c.c. subcutaneously
	6- 3-37	Rational	100.6°	Cloudy	Meningococcus	25 c.c. intrathecally 225 c.c. subcutaneously
	6- 4-37	Improved	99.6°	Slightly cloudy	Sterile	25 c.c. intrathecally 225 c.c. subcutaneously 125 c.c. subcutaneously
	6- 5-37		100.6°	Opalescent	Sterile	15 c.c. intrathecally 110 c.c. subcutaneously 125 c.c. subcutaneously
	6-10-37	No complaint	98.6°	Clear	Sterile	95 c.c. subcutaneously on 6-6 and 150 c.c. on 6-7
Recovered	6-19-37	Discharged	98.4°			40 grains daily from 6-8 to 6-14
No. 3— R. V. A. 5 yrs. male	12-22-37 3rd day of disease	Comatose. Marked nuchal rigidity. Petechiae. Critical	105.0° 106.0° 107.0°	Cloudy 4,900 cells Cloudy	Meningococcus	0.8% Sulfanilamide 12 c.c. intrathecally 110 c.c. subcutaneously 10 c.c. intrathecally 115 c.c. subcutaneously
Died	12-23-37 6 a.m. 6:30 a.m.	Moribund Died	108.0°			

TABLE VII (Continued)

Case	Date	Symptoms		Spinal Fluid		Treatment
		Status of Patient	Temperature	Appearance Cell Count	Bacteriology	
No. 4— C. W. 13 mon. female	1-31-38 4th day of disease	Photophobia irritable strabismus. Positive Kernig. Nuchal rigidity	104.0°	Purulent	Meningococcus	10 grains Sulfanilamide orally
	2- 1-38		103.4°	23,000 cells	Meningococcus	0.8% Sulfanilamide 25 c.c. intrathecally 10 c.c. intrathecally 10 grains orally
	2- 2-38	Blood culture sterile	100.4°	Cloudy	Sterile	5 c.c. intrathecally 10 grains orally
	2- 4-38	Improved	100.4°			10 grains daily orally
	2-10-38	Greatly improved	99.0°	153 cells	Sterile	6 grains daily since 2-4 orally
	2-15-38	Fully recovered		27 cells		
Recovered						
No. 5— C. L. 21 yrs. male	2- 2-38 4th day of disease	Stuporous. Moderate nuchal rigidity	102.0°	280 cells (50% polynuclears)	Meningococcus	40 grains Sulfanilamide orally
	2- 3-38	Lower extremities spastic	105.0°	150 cells	Meningococcus	Antimeningococcic serum 20 c.c. intrathecally 20 c.c. intravenously 60 grains Sulfanilamide orally
	2- 4-38	Condition unchanged	106.0°	Cloudy	Meningococcus	Same as on 2-3
	2- 5-38	Somewhat improved	104.0°	Slightly cloudy	Sterile	Antimeningococcic serum 10 c.c. intrathecally 10 c.c. intravenously 60 grains Sulfanilamide orally
	2- 6-38	Improvement continues. Less rigidity	102.0°	Slightly cloudy	Sterile	Same as on 2-5
	2- 7-38		100.0°	Slightly cloudy		60 grains Sulfanilamide orally
	2- 8-38	Generally improved	99.0°			30 grains Sulfanilamide orally
	2-10-38					Same since 2-8
	2-11-38	Rash, wakeful, probably due to drug	102.0°			Medication stopped
	3-23-38	Patient has been well since 2-13. Residual spasticity has disappeared				
Recovered						

TABLE VII (Continued)

Case	Date	Symptoms		Spinal Fluid		Treatment
		Status of Patient	Temperature	Appearance Cell Count	Bacteriology	
No. 6— H. B. 12 yrs. male	2-15-38 2nd day of disease	Stuporous. Nystagmus. Nuchal rigidity	103.8°	Purulent	Meningo- coccus	0.8% Sulfanilamide 9 c.c. intrathecally 116 c.c. subcutaneously
	2-16-38	Blood culture sterile	106.6°	Purulent	Meningo- coccus	12 c.c. intrathecally 6 c.c. intrathecally 55 grains orally
	2-17-38	Rational	101.0°	Cloudy 1065 cells	Sterile	12 c.c. intrathecally 45 grains orally
	2-19-38	Greatly improved	100.4°	Cloudy	Sterile	30 grains orally
	2-22-38		100.2°	245 cells	Sterile	Same since 2-19
Recovered	2-27-38	Fully recovered				No medication since 2-22-38
No. 7— T. L. 15 mon. male	3-14-38 3rd day of disease	Listless. Nu- chal rigidity. Kernig, bulg- ing fontanelle	102.0°	8,500 cells	Meningo- coccus	10 c.c. intrathecally 115 c.c. subcutaneously 20 c.c. 2.5% Prontosil
	3-15-38		102.6°	Cloudy	Meningo- coccus	10 c.c. intrathecally 115 c.c. subcutaneously 10 c.c. intrathecally 115 c.c. subcutaneously
	3-16-38	Improving	100.0°	Slightly cloudy	Sterile	10 c.c. intrathecally 115 c.c. subcutaneously
	3-17-38		100.0°	Same	Sterile	Same as on 3-15.
	3-18-38	Takes food	101.6°	Opalescent	Sterile	125 c.c. subcutaneously
	3-20-38	Alert	101.0°			125 c.c. subcutaneously 3-20 40 c.c. 2.5% Prontosil 3-19
	3-25-38	Improved	100.0°	27 cells	Sterile	15 grains orally from 3-19
	3-31-38	Fully recovered	98.6°			10 grains orally since 3-25

TABLE VII (Continued)

Case	Date	Symptoms		Spinal Fluid		Treatment
		Status of Patient	Temperature	Appearance Cell Count	Bacteriology	
No. 8— L. A. 42 yrs. female	3-24-38 3rd day of disease	Severe headache. Positive Kernig. Nuchal rigidity absent	100.0°	Purulent	Meningococcus Type I	0.8% Sulfanilamide 30 c.c. intrathecally 175 c.c. subcutaneously 75 gr. orally 40 c.c. 2.5% Prontosil intramuscularly
	3-25-38	Mentally confused	98.4°	Cloudy 3000 cells	Sterile	15 c.c. intrathecally 110 c.c. subcutaneously 75 gr. orally
	3-29-38	Some improvement	100.0°	Gradual reduction to 120 cells	Sterile since 3-25	Same since 3-25
	4- 2-38	Marked improvement in last 3 days. Slight headache today	101.8°	440 cells	Few meningococci	50 grains orally since 3-30
	4- 5-38	Slight nuchal rigidity. Toxic	103.8°	4345 cells	Meningococci	20 c.c. intrathecally 180 c.c. subcutaneously 70 gr. orally since 4-3
	4- 6-38	Same	104.4°	2400 cells	Sterile	Same as 4-5
	4- 7-38	Unchanged. Blood culture sterile	101.2°	332 cells	Sterile	15 c.c. intrathecally 185 c.c. subcutaneously 75 gr. orally
	4- 9-38	Severe anemia	103.0°	2800 cells 2600 cells	Sterile meningococcus	Same since 4-7. Blood transfusion 500 c.c.
	4-10-38	Slightly better	103.6°	Yellow 2400 cells	Meningococcus	Sulfanilamide as above. Antimeningococcic serum 27 c.c. intrathecally 33 c.c. intravenously
	4-11-38	Rigidity more marked	103.4°	4500 cells	Meningococcus	90 gr. Sulfan. orally Meningococcic antitoxin 25 c.c. intrathecally 35 c.c. intravenously
	4-14-38	Generally worse	102.2°	2700 cells	Meningococcus	Therapy same since 4-11
	4-18-38	Stuporous, severe headache Marked nuchal rigidity. Chill	105.0°			Therapy same except that antimeningococcic serum substituted for antitoxin, intraven.
	4-19-38	Projectile vomiting. Involuntaries	103.0°	415 cells	Meningococcus	25 c.c. Sulfan. intrathec. 475 c.c. subcutaneously 30 c.c. serum intraven.
	4-20-38	Condition grave. Blood culture sterile	103.6°	841 cells	Meningococcus	30 c.c. serum intrathec. 45 gr. Sulfan. orally Blood transfusion 300 c.c.
	4-21-38	Died one month from onset of illness				Note—antimeningococcic serum agglutinated the organisms in dilution of 1:800

Died

Six of our eight cases were treated with sulfanilamide alone with one death. One case which recovered was an infant of 15 months who inadvertently received sulfanilamide for six weeks daily without untoward effects. In one of the two cases treated with both sulfanilamide and serum, the drug was at first used with seemingly excellent results, the spinal fluid becoming sterile in 48 hours and the cells dropping from 2470 to 120 with

marked clinical improvement. Though treatment was continued, the patient after about a week relapsed, the cells rose to the thousands and meningococci were again found in smear and culture. With no improvement, antitoxic and antimeningococcic sera were used in large quantities along with sulfanilamide, but the meningococci persisted and after a month's illness, the patient succumbed. The organism was a typical Type 1 meningococcus and it was agglutinated by the antimeningococcus serum used in a dilution of 1:800. In the second case treated with both sulfanilamide and serum, the patient recovered but suffered during convalescence with weakness in one leg and incontinence of urine.

In experimental work upon mice, Brown³⁸ found that the protective influence of 8 mg. of sulfanilamide is comparable to that of 0.1 c.c. of high grade antimeningococcus serum. He also found that the combination of sulfanilamide and serum produced a greater degree of protection than either agent by itself, confirming similar experiments of Branham and Rosenthal.³⁹ Neter⁴⁰ found that sulfanilamide markedly inhibited the growth of meningococci in spinal fluid obtained from patients with meningococcus meningitis.

Altogether, the clinical results in meningococcic meningitis are encouraging but not startling. Patients treated with both serum and sulfanilamide did not seem to do better than those treated with sulfanilamide alone. Nor did treatment with serum alone seem superior to sulfanilamide alone. Other things being equal, sulfanilamide is naturally preferable on the grounds of economy and the absence of serum disease.

Gonococcic Meningitis. Marvin and Wilkinson⁴¹ report a case of gonococcic meningitis first diagnosed meningococcic and treated with antimeningococcus serum. Later with the correct diagnosis sulfanilamide was used. The patient recovered, but the authors are not inclined to give sulfanilamide the credit. The mortality for 22 cases in the literature, not treated with sulfanilamide, was 45 per cent.

Bacillus Proteus Meningitis. Basman and Perley¹⁹ report a case of *Bacillus proteus* meningitis in which the organism was recovered from the blood and the spinal fluid. The patient responded well to sulfanilamide but finally required a mastoidectomy. *Bacillus proteus* was cultured from the mastoid wound. The child made a complete recovery.

DISCUSSION

This survey of various types of meningitis treated with sulfanilamide includes 205 cases from the literature and 22 cases of our own (table 8), a total of 227. The matter is viewed here almost solely as a clinical experiment analogous to experimental work in animals in which the death or survival of the animal is the criterion of the success or failure of the therapeutic experiment. This is feasible because of the almost certain

fatal outcome of all forms of acute meningitis, so that recovery under sulfanilamide of any large group of cases may be reasonably attributed to the drug. Exceptions are taken in meningococcic and gonococcic meningitis in which the mortality with or without other treatment is much lower,

TABLE VIII
Cases of Meningitis Treated with Sulfanilamide

Organism	Number	Recovered	Died
<i>Streptococcus hemolyticus</i>	6	4	2
<i>Streptococcus viridans</i>	2	1	1
<i>Pneumococcus</i>	1	1	0
<i>H. influenzae</i>	2	0	2
<i>Mycobacterium tuberculosis</i>	1	0	1
<i>Neisseria intracellularis</i>	8	6	2
Undetermined	2	1	1
Total	22	13	9

and here conclusions as to the therapeutic worth of the drug must be correspondingly modified.

It is evident at once that no conclusions can be drawn as to the value of sulfanilamide in meningitis as an entity on account of the variation in results in the different types of meningeal infection. Nor can final opinions be given in most instances as to the individual forms of infection until more cases accumulate in the literature. This paper is in part a contribution to that end. It may be said, however, that the value of sulfanilamide in beta hemolytic streptococcus meningitis has been established beyond dispute. A reduction of the mortality from 95 per cent and above to about 20 per cent speaks for itself. Sulfanilamide treated infections due to *Streptococcus viridans*, the tubercle bacillus, or the gonococcus are too few in number for appraisal. The results so far in influenzal meningeal infections are very discouraging. In pneumococcic meningitis with its terrific mortality, the outcome, nine recoveries in 39 cases, at least warrants further trial and seems to offer possibilities. In meningococcic meningitis we collected 84 cases with 11 deaths, a mortality of only 13 per cent, which appears remarkable. Hoyne,³² however, reports only 16 per cent mortality in serum treated cases, and as many of the drug cases also received serum, conclusions should be withheld. As pointed out, if results are equal, sulfanilamide seems preferable.

The experimental work to determine the mode of action of sulfanilamide has emphasized some factors which may have clinical application. Sulfanilamide has little bactericidal effect in vitro ⁴² when added to broth cul-

tures of streptococcus. Lockwood⁴³ found, however, that sulfanilamide in a concentration found in patients receiving the drug will prevent the multiplication of streptococci in cell free normal human serum. And Hoare⁴⁴ states that a considerable bactericidal power was demonstrated in normal human serum to which sulfanilamide has been added in vitro. Osgood³ found in marrow culture experiments with sulfanilamide and streptococci that the drug "did not appear to kill the organisms directly, although it does permit the bactericidal properties of human serum and to some extent phagocytosis by leukocytes to kill organisms which they would otherwise be unable to kill." Brown³⁸ in experimental meningococcus infection found that the combination of sulfanilamide and antimeningococcus serum produced more protection than either agent by itself or by a combination of sulfanilamide and a non-specific serum such as antipneumococcus serum. Branham and Rosenthal³⁹ noted the superiority of combined drug (sulfanilamide) and serum therapy in mice infected with Type 1 pneumococcus. If this serum factor is important in sulfanilamide therapy, then clinically one would expect the best results when a specific antiserum was administered along with the drug. As a matter of fact, this was often done in meningococcus meningitis in which both serum and drug were used, but it cannot be said that the results were more impressive than with the drug alone. Likewise in influenzal meningitis, the cases in which both anti-influenzal serum and sulfanilamide were used did not show noteworthy results. On the other hand, in beta hemolytic streptococcus meningitis in which the very best results were obtained, antiserum was not used. Although in all clinical cases the serum factor may be conceived as playing a participating and perhaps important rôle, the necessity for specific serums in addition to the drug, as suggested by experimental work, has yet to be proved.

The matter of intrathecal treatment with sulfanilamide in these infections might be worthy of comment. There seems to be a tendency in diseases like meningococcus meningitis and tetanus to do away with or minimize intraspinal serum administration with apparently improving results. Of 15 meningococcic patients of Hoyne's⁴⁵ treated intravenously with serum and without any lumbar puncture, only one died. Hoyne³² thinks the intrathecal method of serum therapy prolongs the recovery of the patient. As satisfactory blood and spinal fluid concentrations of sulfanilamide are easily attained by the oral route, it might be better to do away with intrathecal treatment and avoid the possible irritating influence of spinal taps for drainage and injection purposes. Our own tendency would be to minimize intraspinal work.

SUMMARY

This paper is a survey of 227 cases of infectious meningitis, including 22 of our own, treated with sulfanilamide. The results in the various types

of infection are discussed and the part which the simultaneous use of antiserum may play is considered.

ADDENDUM

Since the above paper was submitted, there have been numerous reports of various types of meningitis treated by the sulfonamide group of drugs, particularly the new sulfapyridine.

Toomey and Kimball⁴⁶ report a mortality of 16.6 per cent in 12 cases of hemolytic streptococcus meningitis treated with sulfanilamide. They collected 98 cases, including a number mentioned in our paper, with a mortality of 18 per cent. This is about the same death rate we found with this organism. The figures of Long and Bliss⁴⁷ for hemolytic streptococcus meningitis under the sulfonamide treatment are higher, a mortality rate of 35 per cent.

Results in the treatment of pneumococcic meningitis seem much improved. Allan, Mayer and Williams⁴⁸ report three cases of pneumococcic meningitis in which sulfanilamide was given but no specific antipneumococcic serum. All recovered. Finland, Brown and Rauh⁴⁹ report six recoveries in 10 cases of pneumococcic meningitis. We treated with sulfanilamide and sulfapyridine a type 18 pneumococcic meningitis in an infant of six months. The patient died. MacKeith and Oppenheimer⁵⁰ report two recoveries out of five cases of pneumococcic meningitis treated with sulfapyridine. Hewell and Mitchell⁵¹ obtained four recoveries out of seven cases of pneumococcic meningitis treated with sulfanilamide or related compounds and contrast this with their 100 per cent fatalities in 23 cases before the sulfanilamide era.

We have further treated three cases of influenzal meningitis with sulfanilamide and sulfapyridine combined with serum. There was one recovery. Our impression of the drugs' value was unfavorable.

Branham, Mitchell and Brainin⁵² report a recovery in a case of gonococcic meningitis under sulfanilamide.

Folsom and Gerchow⁵³ (quoted by Long and Bliss) report the unsuccessful treatment of a case of meningitis due to Friedlander's bacillus.

Contributions on meningococcic meningitis are very encouraging. Banks⁵⁴ obtained 15 recoveries in 16 cases treated with sulfanilamide alone. This 6 per cent fatality rate contrasts with 11.8 per cent deaths in 59 cases in which both sulfanilamide and serum were used and 16 per cent mortality with serum alone. Waghestein⁵⁵ likewise had better results with sulfanilamide alone than with combined drug and serum therapy. In 72 adequately treated cases, using the drug only, there was a death rate of 11.59 per cent which, however, is not strikingly lower than his mortality of 16.71 per cent in a large group treated with serum only. Muraz, Chirle and Queguiner⁵⁶ (quoted by Long and Bliss) in an epidemic of meningococcic meningitis among natives of French Nigeria had only 10.7 per cent fatalities in 271 patients treated with sulfanilamide alone, 8.7 per cent deaths when using a combination of serum and sulfanilamide in 23 patients and 14.8 per cent deaths when employing intrathecal injections along with sulfanilamide by mouth. They contrast this with 74.6 per cent deaths in 8,653 patients afflicted with the disease in the presulfanilamide days. In the Anglo-Egyptian Sudan, where conditions are very unfavorable and the mortality usually from 65 to 70 per cent, Somers⁵⁷ treated 143 consecutive cases with sulfapyridine, with a mortality of 10 per cent. In the same district, Bryant and Fairman⁵⁸ treated 21 cases with sulfanilamide and 168 patients with sulfapyridine. The death rate in both series was but 5 per cent.

The trend of opinion as to the action of the sulfonamide drugs seems to be that there is some interference with bacterial metabolism or nutrition whereby bacterial growth is prevented or retarded, thus allowing the normal or immune defense mecha-

nism to handle the situation adequately.^{59, 60} In general, the tendency in meningitis treatment is to avoid intrathecal medication and spinal drainage or frequent spinal taps.^{46, 55}

REFERENCES

1. GAY, F. P., and CLARK, A. R.: On the mode of action of sulfanilamide in experimental streptococcus empyema, Jr. Exper. Med., 1937, lxvi, 535.
2. BLISS, E. A., and LONG, P. H.: Observations on the mode of action of sulfanilamide, Jr. Am. Med. Assoc., 1937, cix, 1524.
3. OSGOOD, E. E.: Culture of human marrow. Studies on the mode of action of sulfanilamide, Jr. Am. Med. Assoc., 1938, cx, 349.
4. TRIPOLI, C. J.: Bacterial meningitis, Jr. Am. Med. Assoc., 1936, cvi, 171.
5. GRAY, H. J.: Streptococcic meningitis, Jr. Am. Med. Assoc., 1935, cv, 92.
6. LONG, P. H., and BLISS, E. A.: The clinical uses of sulfanilamide and its derivatives in the treatment of infectious diseases, ANN. INT. MED., 1937, xi, 575.
7. CANFIELD, N.: Streptococcus meningitis, report of a case with recovery, Jr. Michigan Med. Soc., 1933, xxxii, 108.
8. ZELIGS, M.: Streptococcic meningitis, report of 2 cases with recovery, Am. Jr. Dis. Child., 1935, l, 1497.
9. SCHWENTKER, F. F. ET AL.: The use of para-amino-benzene-sulphonamide or its derivatives in the treatment of beta hemolytic streptococcal meningitis, Bull. Johns Hopkins Hosp., 1937, lx, 297.
10. NEAL, J. B., and APPLEBAUM, E.: Experience with sulfanilamide in meningitis, Am. Jr. Med. Sci., 1938, cxcv, 175.
11. APPLEBAUM, E.: Personal communication.
12. TRACHSLER, W. H. ET AL.: Streptococcic meningitis, with special emphasis on sulfanilamide therapy, Jr. Pediat., 1937, xi, 248.
13. CAREY, B. W., JR.: The use of para-amino-benzene-sulfonamide and its derivatives in the treatment of infections due to the beta *Streptococcus hemolyticus*, the meningococcus, and the gonococcus, Jr. Pediat., 1937, xi, 202.
14. NEAL, J. B., JACKSON, H. W., and APPLEBAUM, E.: A comprehensive study of meningitis secondary to otitic or sinus infection, Ann. Otol., Rhin. and Laryngol., 1934, xliii, 658.
15. MELLON, R. R., and COOPER, F. B.: The biphasic nature of certain alpha-prime (?) hemolytic streptococci, Proc. Soc. Exper. Biol. and Med., 1938, xxxviii, 158.
16. MERTINS, P. S., and MERTINS, P. S., JR.: Meningitis due to the Type 4 pneumococcus, with recovery, Arch. Otolaryngol., 1937, xxv, 657.
17. CALDWELL, J. R., and BYRNE, P. S.: Recovery from pneumococcal meningitis, Brit. Med. Jr., 1937, i, 1204.
18. MITCHELL, A. GRAEME, and TRACHSLER, W. H.: Report on the use of sulfanilamide and its derivatives at the Children's Hospital of Cincinnati, Jr. Pediat., 1937, xi, 183.
19. BASMAN, J., and PERLEY, A. M.: Report of patients treated with sulfanilamide at the St. Louis Children's Hospital, Jr. Pediat., 1937, xi, 212.
20. FOTHERGILL, L. D.: Hemophilus influenzae (Pfeiffer bacillus) meningitis and its specific treatment, New England Jr. Med., 1937, ccxvi, 587.
21. SILVERTHORNE, N., FRASER, D. T., and SNELLING, C. E.: Influenzal meningitis, Jr. Pediat., 1937, x, 228.
22. SCHWENTKER, F. F.: Quoted by Fothergill—personal communication.
23. MCINTOSH, R., WILCOX, D. A., and WRIGHT, F. H.: Results of sulfanilamide treatment at the Babies' Hospital, New York City, Jr. Pediat., 1937, xi, 167.
24. McQUARRIE, I.: Report of cases treated with sulfanilamide (prontosil and prontylin), Jr. Pediat., 1937, xi, 187.
25. HAGEMAN, P. O.: Clinical experience in the use of sulfanilamide at the New Haven Hospital, Jr. Pediat., 1937, xi, 195.

26. RICH, A. R., and FOLLIS, R. H., JR.: The inhibitory effect of sulfanilamide on the development of experimental tuberculosis in the guinea pig, *Bull. Johns Hopkins Hosp.*, 1938, lxii, 77.
27. SCHWENTKER, F. F., GELMAN, S., and LONG, P. H.: The treatment of meningococcic meningitis with sulfanilamide, *Jr. Am. Med. Assoc.*, 1937, cviii, 1407.
28. McDONALD, J. R., HENTHORNE, J. C., and THOMPSON, L.: Role of anaerobic streptococci in human infections, *Arch. Path.*, 1937, xxiii, 230.
29. SMITH, F. W. ET AL.: Anaerobic beta hemolytic streptococcus meningitis of otitic origin treated with sulfanilamide and culminating in complete recovery, *Jr. Am. Med. Assoc.*, 1938, cx, 887.
30. United States Public Health Reports, December, 1934, 1935.
31. LEVY, G. H.: Meningococcus meningitis, report of 176 cases treated with Ferry's antitoxin, *Jr. Pediat.*, 1937, xi, 868.
32. HOYNE, A. L.: Intravenous treatment of meningococcic meningitis with meningococcus antitoxin, *Jr. Am. Med. Assoc.*, 1936, cvii, 478.
33. SCHWENTKER, F. F.: Treatment of meningococcus meningitis with sulfanilamide, *Jr. Pediat.*, 1937, xi, 874.
34. BERNSTEIN, S. S.: Report on the use of sulfanilamide at the Children's Hospital of Michigan, *Jr. Pediat.*, 1937, xi, 199.
35. CAREY, B. W., JR.: The use of para-aminobenzenesulfonamide and its derivatives in the treatment of infections due to the beta hemolytic streptococcus, the meningococcus and the gonococcus, *Jr. Pediat.*, 1937, xi, 202.
36. BRENNEMAN, J.: Report on sulfanilamide from the Children's Memorial Hospital of Chicago, *Jr. Pediat.*, 1937, xi, 239.
37. WILLIEN, L. J.: Sulfanilamide therapy in meningococcic meningitis, *Jr. Am. Med. Assoc.*, 1938, cx, 630.
38. BROWN, T. M.: Protective action of sulfanilamide and antimeningococcus serum on meningococcus infection of mice, *Bull. Johns Hopkins Hosp.*, 1937, lxi, 272.
39. BRANHAM, S. E., and ROSENTHAL, S. M.: Studies in chemotherapy. Sulfanilamide, serum and combined drug and serum therapy in experimental meningococcus and pneumococcus infections in mice, *Pub. Health Rept.*, 1937, lii, 685.
40. NETER, E.: Bacteriostatic action of sulfanilamide upon meningococcus in spinal fluid, *Proc. Soc. Exper. Biol. and Med.*, 1938, xxxviii, 37.
41. MARVIN, H. P., and WILKINSON, W. E.: Gonococcic meningitis, results of treatment with sulfanilamide, *Jr. Am. Med. Assoc.*, 1938, cx, 800.
42. COLEBROOK, L., BUTTLE, G. A. H., and O'MEARA, R. A. Q.: The mode of action of para-aminobenzenesulphonamide and prontosil in hemolytic streptococcal infections, *Lancet*, 1936, ii, 1323.
43. LOCKWOOD, J. S.: Personal Communication.
44. HOARE, E. D.: Bactericidal changes induced in human blood and serum by sulphanido-chryspodine and sulphanilamide, *Lancet*, 1938, i, 655.
45. HOYNE, A. L.: Meningococcus meningitis, *Jr. Pediat.*, 1937, xi, 863.
46. TOOMEY, JOHN A., and KIMBALL, E. ROBBINS, JR.: Meningitis caused by Streptococcus haemolyticus and treated with sulfanilamide, *Jr. Am. Med. Assoc.*, 1939, cxii, 2586.
47. LONG, P. H., and BLISS, E. A.: The clinical and experimental use of sulfanilamide, sulfapyridine and allied compounds, 1939, The Macmillan Company, New York.
48. ALLAN, W. B., MAYER, S., JR., and WILLIAMS, R.: Pneumococcus meningitis with recovery; report of 3 cases, *Am. Jr. Med. Sci.*, 1938, cxcvi, 99.
49. FINLAND, M., BROWN, J. W., and RAUH, A. E.: Treatment of pneumococcic meningitis; study of 10 cases treated with sulfanilamide alone or in various combinations with specific antipneumococcic serum and complement, including 6 recoveries, *New England Jr. Med.*, 1938, ccxviii, 1033.
50. MACKEITH, RONALD C., and OPPENHEIMER, G.: Pneumococcal meningitis. Report on five consecutive cases treated with sulphanilamide-pyridine (M. & B. 693), *Lancet*, 1939, i, 1099.

51. HEWELL, B. A., and MITCHELL, A. G.: Treatment of pneumococcic meningitis with sulfanilamide; review of literature and report of 6 additional cases, *Jr. Am. Med. Assoc.*, 1939, cxii, 1033.
52. BRANHAM, S. E., MITCHELL, R. H., and BRAININ, W.: Gonococcic meningitis, *Jr. Am. Med. Assoc.*, 1938, cx, 1804.
53. FOLSOM, T. G., and GERCHOW, K. E.: Influenzal meningitis successfully treated with sulfanilamide, *West Virginia Med. Jr.*, 1938, xxxiv, 254.
54. BANKS, H. STANLEY: Serum and sulphanilamide in acute meningococcal meningitis; preliminary survey based on 113 cases, *Lancet*, 1938, ii, 7.
55. WAGHELSTEIN, J. M.: Sulfanilamide in treatment of 106 patients with meningococcic infections, *Jr. Am. Med. Assoc.*, 1938, cxi, 2172.
56. MURAZ, G., CHIRLE, H., and QUEGUINER, A.: Essais comparés de traitements (sérum; corps azoïque; sulfanilamide) de la méningite cérébro-spinale dans des régions coloniales rurales (Niger français), *Presse méd.*, 1938, xlvii, 1113.
57. SOMERS, R. B. USHER: M. & B. 693 in cerebrospinal fever. A review of 143 cases treated under field conditions, *Lancet*, 1939, i, 921.
58. BRYANT, J., and FAIRMAN, H. D.: Chemotherapy of cerebrospinal fever in the field, *Lancet*, 1939, i, 923.
59. LONG, P. H., BLISS, E. A., and FEINSTONE, W. H.: Mode of action, clinical use and toxic manifestations of sulfanilamide; further observations, *Jr. Am. Med. Assoc.*, 1939, cxii, 115.
60. McINTOSH, J., and WHITBY, L. E. H.: Mode of action of drugs of sulphonamide group, *Lancet*, 1939, i, 431.

FIVE YEARS' EXPERIENCE (1933-1937) WITH MORTALITY FROM ACUTE CORONARY OCCLUSION IN PHILADELPHIA *

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OVER a quarter of a century has passed since Herrick¹ in 1912 directed the attention of the medical profession to the clinical diagnosis of acute coronary occlusion. Although a few men before Herrick had diagnosed this condition antemortem, he was the first to focus interest on this now well recognized clinical entity. In the words of Sir William Osler,² "In science the credit goes to the man who convinces the world, not to the man to whom the idea first occurs."

During the period since 1919³ studies have been made of this disease from nearly every conceivable point of view. Studies of mortality from coronary disease have consisted for the most part in attempts to reconstruct diagnoses made in the past to fit modern conceptions of this disease. This is the first attempt to analyze deaths reported as due to acute coronary occlusion in a large city over a period of several years.

During the period from January 1, 1933 to December 31, 1937, 5116 deaths were reported by physicians in Philadelphia as due to acute coronary occlusion, coronary thrombosis, and other practically synonymous terms. So far as was possible this study was limited to deaths apparently due to an acute coronary "accident," the result of coronary atherosclerosis. Deaths indicated as due to coronary sclerosis and other chronic degenerative diseases were excluded, as were also deaths certified as due to syphilitic involvement of the coronary arteries or to coronary embolus in rheumatic heart disease or subacute bacterial endocarditis.

Sources of Material. Of these 5116 deaths, 703, or 13.7 per cent, occurred among patients regularly admitted to 26 civilian hospitals approved for internship by the American Medical Association; 1868, or 36.5 per cent, were coroner's cases; and 2545, or 49.8 per cent, were reported from all other sources (table 1). Of these, 2440 deaths occurred in the homes, while 105 occurred in hospitals other than those mentioned. For practical purposes this group may be regarded as composed of deaths reported by practicing physicians. Of the deaths occurring in hospitals, 197 diagnoses were confirmed by postmortem findings.

The age distribution and mean ages at deaths from these three sources differed to a certain extent. Coroner's cases indicated the youngest age distribution, with a peak incidence in the 50-59 year age decade (figure 1).

* Read at the New Orleans meeting of the American College of Physicians March 28, 1939.

From the Office of Heart Disease Investigations. National Institute of Health, United States Public Health Service. Branch Office, 133 S. 36th St., Philadelphia, Pa.

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The mean age at death among coroner's cases was 58.1 years. Among all other groups studied the maximum number of deaths occurred in the 60-69 year age period. The mean age of deaths occurring among patients regularly admitted (exclusive of coroner's cases) to 26 civilian hospitals ap-

TABLE I

Number of Deaths Attributed to Acute Coronary Occlusion in Philadelphia Each Year from January 1, 1933 to December 31, 1937, among Patients Regularly Admitted to 26 Civilian Hospitals Approved for Internship by the American Medical Association, Coroner's Cases, Deaths Reported from All Other Sources, and the Total Number of Deaths Attributed to This Cause

Year	Deaths in Civilian Hospitals Approved for Internship by the American Medical Association	Coroner's Cases	Deaths in Other Hospitals and in the Homes	Total
1933	114	258	300	672
1934	96	299	408	803
1935	159	383	454	996
1936	140	403	581	1124
1937	194	525	802	1521
Total	703	1868	2545	5116
Percentage of total	13.7	36.5	49.8	100.0
Percentage increase in 5 years	70	103	167	126

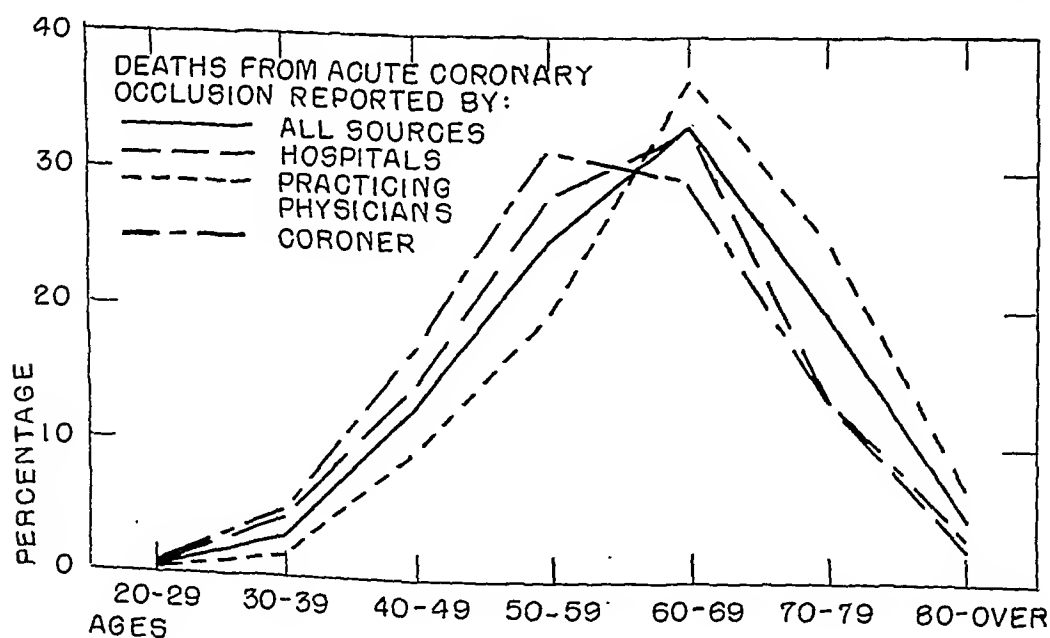


FIG. 1. Percentage age distribution by decades of life of 5116 deaths reported as due to acute coronary occlusion, 703 deaths reported from 26 civilian hospitals approved for internship by the American Medical Association, 1868 coroner's cases and 2545 deaths from other sources, most of which occurred in the homes, in Philadelphia from January 1, 1933 to December 31, 1937.

proved for internship by the American Medical Association was 59.5 years; among necropsied cases 59.8 years. The mean age of deaths attributed to this cause and occurring in the homes was 63.9 years. The mean age of the entire series of 5116 deaths was 62.1 years.

The fact that the mean ages at death of cases occurring in the homes was older by more than four years than deaths in hospitals was only to be expected. An even greater difference was noted among deaths from rheumatic heart disease.⁴ It occurs chiefly because elderly persons are not as frequently admitted to hospitals.

Accuracy of Diagnoses. While it is not possible for a statistical analyst reviewing a large series of cases to determine the accuracy of diagnosis in each fatal case, efforts should be made to compare the age distribution with that observed and reported from sources believed to be reliable. In figure 2

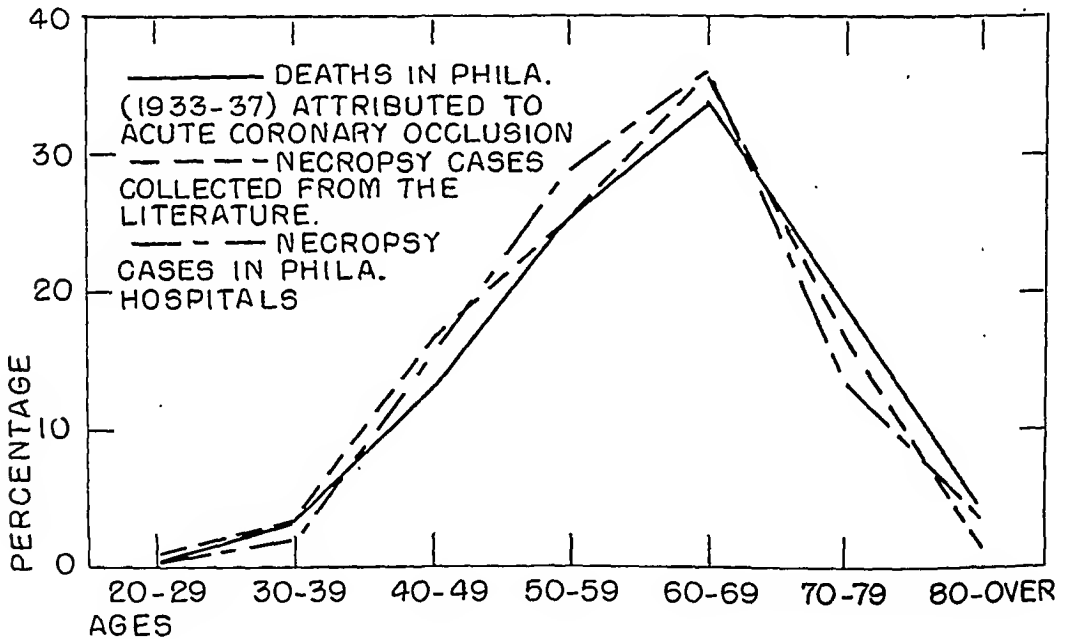


FIG. 2. Percentage age distribution, by decades of life, of 5116 deaths reported as due to acute coronary occlusion in Philadelphia from January 1, 1933 to December 31, 1937, compared with 284 necropsied cases collected from the literature and 197 fatal cases in this series in which the diagnoses were based on necropsy findings.

a comparison is made of these 5116 deaths with 197 deaths in hospitals, in which the diagnoses were confirmed by postmortem examinations and with 284 necropsy cases collected from the literature, consisting of the combined studies of Levine,⁵ Saphir et al.,⁶ Applebaum and Nicolson,⁷ and Meakins and Eakin.⁸ The age distribution of deaths reported as due to acute coronary occlusion in Philadelphia during these five years compares quite closely with the age distribution observed in these two series based on postmortem findings.

In figure 3 is shown the age distribution and mean ages at death during each year of the quinquennium under study. Despite an increase of 126

per cent in the total number of deaths reported in 1937 as compared with 1933, the age distribution is so nearly the same that the lines in this figure are nearly indistinguishable. The mean ages at death varied only 1.8 years during this period. As a corollary to this lack of variability in the age distribution, it seems apparent that the increase in reported mortality cannot be attributed to a tendency to report more deaths among very old persons as due to this cause.

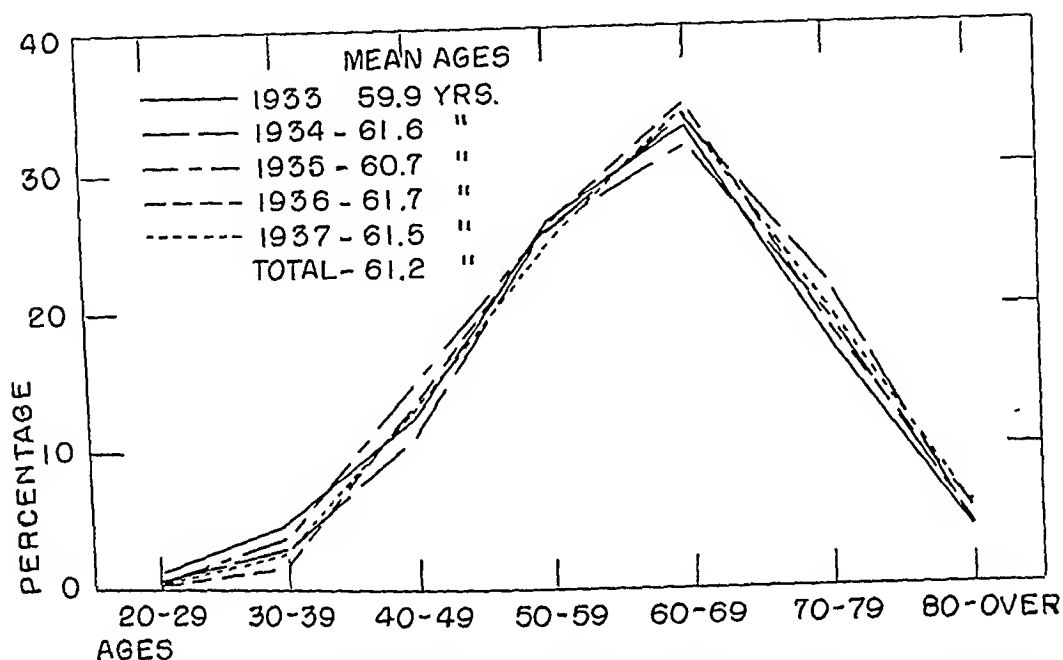


FIG. 3. Percentage age distribution, by decades of life, and mean ages at death of 5116 deaths reported as due to acute coronary occlusion in Philadelphia based on the number of deaths occurring in each of the five years under study.

This is further illustrated by a comparison of deaths attributed to acute coronary occlusion with deaths from all heart disease (table 2). In the age period 50-59 years 26.0 per cent of the deaths reported as due to heart disease were attributed to acute coronary occlusion. This percentage declines with each succeeding decade so that in the age period past 80 years of age only 5.5 per cent of all deaths from heart disease were reported as due to acute coronary occlusion. Furthermore, while the age specific death rates from all forms of heart disease increased precipitously in the age periods past 70 years of age, the age specific mortality rates from acute coronary occlusion showed a very gradual increase.

Of the total deaths attributed to this cause only 24.5 per cent occurred among persons past 70 years of age, while among deaths from all heart disease during this five-year period 42.1 per cent occurred among persons past 70 years of age. Of the deaths from coronary occlusion occurring in hospitals only 19.1 per cent occurred among persons over 70 years of age. Even among deaths occurring in the homes only 31.9 per cent were over

70 years of age. On the other hand, of the total deaths attributed to acute coronary occlusion, 41.1 per cent occurred among persons younger than 60 years of age. As depicted in the general mortality returns, acute coronary occlusion is primarily a problem of the 40-69 year age period.

In the opinion of the writer, acute coronary occlusion is not being used in Philadelphia as a blanket diagnosis of deaths among persons in advanced age periods. Although there were doubtless some incorrect diagnoses, the age distribution conforms quite closely to the accepted age distribution of this disease. For the most part, these diagnoses appeared to have been made with an attempt to portray a definite clinical condition.

TABLE II

Comparison of Number of Deaths and Age Specific Death Rates from Acute Coronary Occlusion with Reported Mortality from All Heart Disease in Philadelphia from January 1, 1933 to December 31, 1937 (Based on the U. S. Census of 1930)

Age Groups	Population	Deaths from Coronary Occlusion	Mean Annual Specific Death Rate per 100,000 Population	Deaths from All Forms of Heart Disease	Mean Annual Specific Death Rate per 100,000 Population	Percentage of Total Heart Disease Due to Acute Coronary Occlusion
20-29	356,592	21	1	483	27	4.3
30-39	333,058	160	10	1,100	66	14.5
40-49	259,787	663	51	2,817	217	23.5
50-59	181,963	1,299	143	4,992	549	26.0
60-69	108,545	1,720	317	8,492	1,565	20.3
70-79	44,083	1,003	455	8,508	3,860	11.8
80 and over	10,165	248	488	4,474	8,803	5.5
Total	1,294,193	5,114*		30,866		

* 2 ages unknown.

Race and Sex Distribution. These studies indicate a much lower mortality from acute coronary occlusion among Negroes as compared with white persons. The mean annual death rate was 56 per 100,000 white persons as compared with 21 per 100,000 Negroes. The lower mortality rate among Negroes is not entirely due to a younger age distribution of the colored population, since the mean annual age specific death rates by decades of life are lower among Negroes than among white persons (table 3). While this may be due in part to less accurate diagnoses of acute coronary occlusion among colored people, it is probably more than offset by the mis-diagnosis of more cases of syphilitic cardiovascular disease as acute coronary occlusion.

Only 231, or 4.5 per cent of the 5116 deaths reported as due to acute coronary occlusion occurred among colored persons (table 4). According to the U. S. Census of 1930, Negroes accounted for 11.3 per cent of the population of Philadelphia. Of the deaths from acute coronary occlusion among regularly admitted patients to 26 civilian hospitals approved for internship by the American Medical Association, only 5.7 per cent were

TABLE III

Number of Deaths and Mean Annual Age Specific Death Rates by Age Decades per 100,000 Population from Acute Coronary Occlusion According to Color of Decedents in Philadelphia for the Period from January 1, 1933 to December 31, 1937
(Based on the U. S. Census of 1930)

Age Decade (years)	Total—Both Races			White			Colored		
	Population	Deaths	Mean Annual Rate per 100,000	Population	Deaths	Mean Annual Rate per 100,000	Population	Deaths	Mean Annual Rate per 100,000
20-29.....	356,592	21	1	306,339	15	1	50,253	6	2
30-39.....	333,058	160	10	285,323	132	9	47,735	28	12
40-49.....	259,787	663	51	229,663	605	53	30,124	58	39
50-59.....	181,963	1299	143	167,316	1222	146	14,647	77	105
60-69.....	108,545	1720	317	103,446	1675	324	5,099	45	177
70-79.....	44,083	1003	455	43,429	990	467	1,654	13	157
80 and over.....	10,165	248	488	9,704	244	503	461	4	174
Total over age 20 yrs.....	1,294,193	5114*	79	1,144,220	4883	85	149,973	231	31

* 2 deaths with ages unknown.

TABLE IV

Number and Percentage of Deaths in Each Age Decade and Mean Age at Death According to Color and Sex among 5116 Deaths Attributed to Acute Coronary Occlusion in Philadelphia (from All Sources) from January 1, 1933 to December 31, 1937

Age Decade (years)	Total						White						Colored					
	Both Sexes		Male		Female		Both Sexes		Male		Female		Both Sexes		Male		Female	
	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent
	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent
20-29.....	21	.4	10	.3	11	.6	15	.3	8	.3	7	.4	6	2.6	2	1.6	4	3.7
30-39.....	160	3.1	107	3.2	53	3.0	132	2.7	91	2.8	41	2.5	28	12.1	16	12.9	12	11.2
40-49.....	663	13.0	521	15.4	142	8.2	605	12.4	487	15.0	118	7.3	58	25.1	34	27.5	24	22.4
50-59.....	1299	25.4	952	28.2	347	20.0	1222	25.0	910	28.0	312	19.1	77	33.3	42	33.8	35	32.7
60-69.....	1720	33.6	1111	32.9	609	35.0	1675	34.3	1092	33.6	583	35.7	45	19.6	19	15.3	26	24.4
70-79.....	1003	19.6	566	16.8	437	25.1	990	20.3	556	17.0	434	26.6	13	5.6	10	8.1	3	2.8
80 and over.....	248	4.9	108	3.2	140	8.1	244	5.0	107	3.3	137	8.4	4	1.7	1	.8	3	2.8
Unknown...	2		2		0		2		2		0		0		0		0	
Total.....	5116	100	3377	100	1739	100	4885	100	3253	100	1632	100	231	100	124	100	107	100
Percentage of total...		100		66.0		34.0		95.5		63.6		31.9		4.5		2.4		2.1
Mean ages at death..	61.2		59.8		63.9		61.6		60.0		64.7		52.3		52.0		52.7	

among Negroes. This occurs despite the fact that due to their less fortunate economic status, Negroes account for a disproportionately large part of the hospital admissions for all causes.

Although coronary occlusion appeared to be less frequent among Negroes, the age distribution and mean ages indicated deaths at considerably younger ages. The mean age at death among white persons in the series

as a whole was 61.6 years as compared with 52.3 years among Negroes. Among the 703 deaths in hospitals, the mean age at death among white persons was 60.1 years as compared with 49.0 years among Negroes. The few necropsy cases among Negroes also supported this view.

Among deaths attributed to acute coronary occlusion from the city as a whole, the mean age among males was 59.8 years, as compared with 63.9 years among females, more than four years older than the males. Of the deaths in hospitals the mean age among males was 60.1 years as compared with 59.1 years among females. Since there is an element of selection of cases dying in hospitals, the mean ages at death in the entire city are probably more accurate. The age distribution also indicated deaths at younger ages among males.

The ratio of males to females was approximately 2 to 1. This is lower than has been reported in other series and may be due to relatively more females past 70 years of age. It is noteworthy, however, that of the deaths among patients regularly admitted to hospitals the ratio of males to females was only 1.7 to 1. Among the coroner's cases, however, the ratio was 3.6 to 1. Since over 95 per cent of the deaths attributed to this disease occurred among white persons, the ratio of deaths among males as compared with females was about the same as for the entire series. Among Negroes, however, there were nearly as many deaths among females as among males reported as due to this cause.

A more complete analysis of these 5116 deaths attributed to this cause, with tables giving detailed information concerning cases occurring in hospitals, in the homes, coroner's cases, and diagnoses confirmed by necropsy will be reported in another publication.⁹

Monthly Distribution. In general, the distribution of deaths from this cause by months corresponded to the monthly distribution of deaths from all heart disease and of deaths from all causes (figure 4). There were only 53 per cent as many deaths from acute coronary occlusion in August as in December. Although the seasonal variation in deaths from this cause is not as marked as in deaths from certain infectious diseases, the number of deaths was appreciably lower during the summer months.

Countries of Birth. The mean age at death was more advanced among persons born in Germany among whom it was 66.7 years and youngest among Italians among whom it was 57.2 years. Deaths among other foreign born persons ranged between these two extremes. Among native born white Americans the mean age at death was 61.7 years. The mean age at death among foreign born persons depended largely on the period in which the greatest amount of immigration occurred. Among foreign born persons from countries from which the immigration was the greatest prior to 1900, the mean ages at death indicated deaths at older age periods than among persons from countries from which immigration was largest subsequent to that time. It is doubtful if nationality plays an important rôle in determining the age at death.

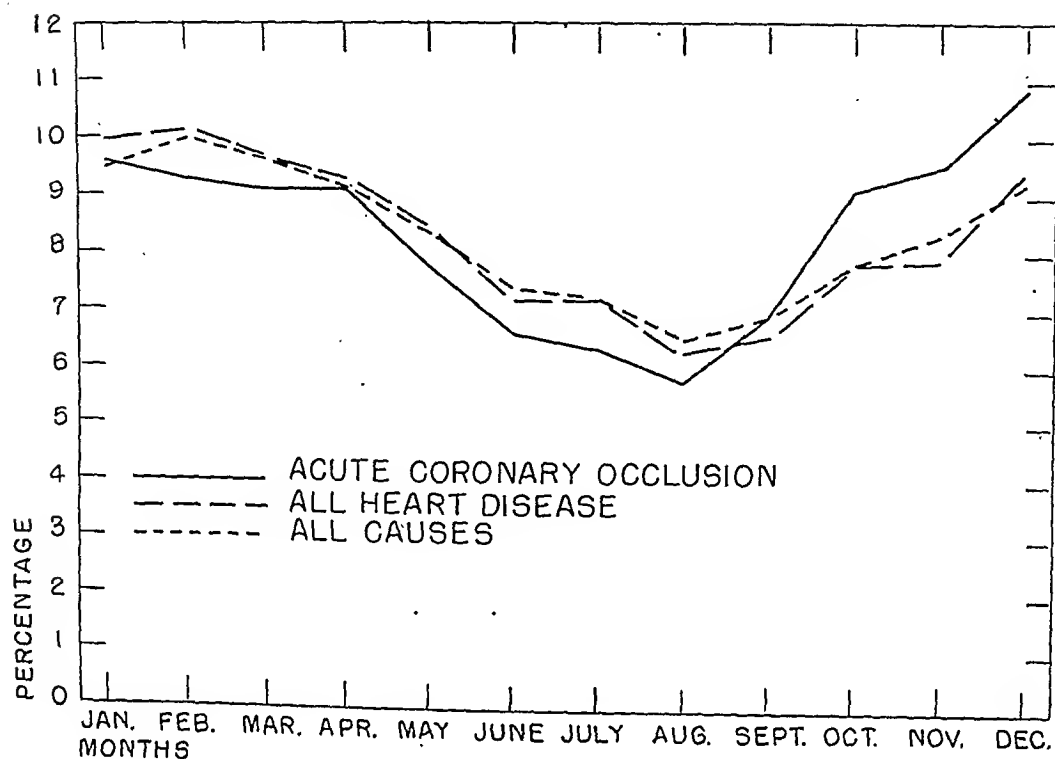


FIG. 4. Percentage distribution of deaths from acute coronary occlusion by months (adjusted to a 30-day basis) as compared with deaths from all causes and from all heart disease in Philadelphia from January 1, 1933 to December 31, 1937.

The age specific death rate according to nations of birth indicated considerably higher death rates among persons born in Russia and in Austria-Hungary than among persons born in other foreign countries or among native born white Americans (table 5). This was especially notable in the

TABLE V

Number of Deaths during the Five-Year Period and Mean Annual Age Specific Death Rates per 100,000 Population from Acute Coronary Occlusion among White Persons in 20 Year Periods among Persons over 25 Years of Age in Philadelphia from January 1, 1933 to December 31, 1937, Based on Certain Countries of Birth (From U. S. Census of 1930)

Country of Birth	Total over 25 Yrs. of Age			25-44 Years of Age			45-64 Years of Age			65 Years and over		
	Population	Deaths	Mean Annual Rate per 100,000	Population	Deaths	Mean Annual Rate per 100,000	Population	Deaths	Mean Annual Rate per 100,000	Population	Deaths	Mean Annual Rate per 100,000
United States.....	650,478	2904	89	389,993	247	13	202,169	1428	141	58,316	1229	421
Russia.....	72,310	603	167	40,459	32	16	26,998	393	291	4,853	178	734
Germany.....	34,132	252	148	11,642	7	12	14,739	83	113	7,721	162	420
Ireland.....	48,091	271	113	16,546	6	7	22,994	123	107	8,551	142	332
Austria-Hungary.....	16,553	128	155	8,800	10	23	6,723	76	226	1,030	42	816
Italy.....	61,118	182	60	35,527	16	9	21,329	121	113	4,262	45	211
England, Scotland and Wales.....	32,089	197	123	12,234	7	11	14,339	73	102	5,516	117	424
Poland.....	28,358	82	58	17,264	6	7	9,745	53	109	1,349	23	341

45-64 year age period, in which the mean annual death rate was 291 per 100,000 persons of Russian birth and 226 per 100,000 persons of Austrian birth. Among native born white Americans it was only 141 per 100,000 persons and among persons born in Ireland, Germany, Poland, and Great Britain it was even less.

Ninety-seven per cent of the deaths from this cause among persons born in Russia were among Hebrews. Based on rather incomplete returns the mean annual death rate was 67 per 100,000 Jewish persons as compared with 53 per 100,000 non-Jewish white persons. It seems likely that the mortality from acute coronary occlusion is slightly higher among all Jewish persons than among Gentiles. It is doubtful, however, if it is much higher among native born Jews than among white Gentiles.

Occupations of Decedents. During 1935-36, the United States Public Health Service conducted a National Health Survey. In Philadelphia, 122,270 persons, or about 6 per cent of the population, were enumerated. This group may be assumed to be a roughly representative sample of the population of Philadelphia as to age, race, sex and economic status. This sample included 18,417 white males between 35-64 years of age.

By determining the number of persons in each broad occupational group in each 10-year age period, and applying this sample to the total white male population in this age period, it is possible to estimate the number of professional men, proprietors, managers and officials, clerks and salesmen, and workers of all classes including foremen in each 10-year period among the white male population between 35-64 years of age. This is the age period among gainfully employed persons in which deaths from this cause are most common. By applying the same occupational code to the occupations listed on death certificates it is possible to estimate the age specific mortality rates per 100,000 persons in each occupational group.

Based on this estimate, the mean annual mortality rate in the age period 35-64 years was 154 per 100,000 professional men, 140 per 100,000 proprietors, managers and officials, 128 per 100,000 clerks and salesmen and only 107 per 100,000 workers (table 6). In the 55-64 year age decade the estimated mean annual mortality rate was 475 per 100,000 professional men, 357 per 100,000 clerks and salesmen, 304 per 100,000 proprietors, managers and officials, and 253 per 100,000 workers.

Caution is suggested in interpreting too literally the high mortality rate from acute coronary occlusion among professional men. It is possible that higher standards of diagnosis prevailed among this occupational group. It is difficult to understand, however, why the standards of diagnosis should be higher among this group, with the exceptions of physicians, than among business men. This study should be repeated at the end of another five-year period when the diagnosis of this condition has had an opportunity to become better stabilized among all occupational and social classes. It is interesting to note that such estimates as are available at the present time

indicate a higher incidence of this disease among professional men and the lowest incidence among workers.

Is Acute Coronary Occlusion Increasing? During the quinquennium under study the number of deaths attributed to this cause increased 126 per cent. Is this increase genuine? To what extent is it fictitious? What factors, other than an actual increase, may be invoked to explain why more deaths were reported each year as due to this cause? Have general practitioners become sufficiently adept in the diagnosis of acute coronary occlusion to permit many definite conclusions?

TABLE VI

Estimated Number of White Males between 35-64 Years of Age in Each Occupational Group by 10-year Age Periods, Number of Deaths from Acute Occlusion among White Males between 35-64 Years of Age by 10-year Age Periods According to Occupation, and the Estimated Mean Annual Age Specific Mortality Rates per 100,000 Persons in Each Occupation Group in Philadelphia from January 1, 1933 to December 31, 1937.
Deaths Are Listed on a Five-Year Basis

Occupational Groups	35-44 Years			45-54 Years			55-64 Years			Total: 35-64 Years		
	Estimated Population	No. of Deaths	Estimated Mean Annual Death Rate	Estimated Population	No. of Deaths	Estimated Mean Annual Death Rate	Estimated Population	No. of Deaths	Estimated Mean Annual Death Rate	Estimated Population	No. of Deaths	Estimated Mean Annual Death Rate
Professional men....	7,684	18	47	5,145	28	109	3,284	78	475	16,113	124	154
Proprietors, managers, and officials..	18,462	34	37	17,144	129	150	10,463	159	304	46,069	322	140
Clerks and salesmen..	25,915	47	36	14,780	109	147	9,139	163	357	49,834	319	128
Workers—all classes..	81,641	118	29	59,677	371	124	36,083	456	253	177,401	945	107
Total.....	133,702	217	32	96,746	637	132	58,969	856	290	289,417	1710	118

These and many other questions present themselves. It is doubtful if any of them can be answered categorically at this time. It is well to take stock, even though it is not possible to make a complete inventory of all of the factors involved. In attempting to arrive at some conclusions, certain possible considerations will be reviewed for the purpose of elimination. Having disposed of them, the remaining factors will be considered in greater detail:

1. The increase in reported mortality is not due to an undue tendency to report deaths among persons past 70 years of age as due to this cause. The reported mortality compares quite closely to the age distribution of diagnoses confirmed at necropsy. The age distribution remained practically the same during these five years under study.

2. Conversely, the increase was not due to relatively more deaths occurring in age periods prior to 60 years.

3. Although the aging of the population was doubtless a factor, it was not sufficient to account for an increase of 126 per cent in five years. Deaths from all causes, and from such diseases as cancer, diabetes mellitus,

and all heart disease did not increase to that extent. Furthermore, acute coronary occlusion did not appear to be primarily a problem of the aged.

4. The increase cannot be attributed, to any appreciable extent, to the aging of the foreign born population, over and above the aging of the general population. Deaths attributed to this cause increased 141 per cent in the period under study among the native born population, but only 132 per cent among the foreign born population.

5. The increase could not be explained on the basis of changes of terminology in diagnosis. According to the records of the Philadelphia Health Department there were only 10 per cent fewer deaths attributed to angina pectoris in 1937 than in 1933, while deaths attributed to all forms of coronary disease increased nearly 100 per cent.

This leaves two important considerations: improvement in diagnosis and the possibility of an actual increase. Of these two factors, better diagnosis appears to be the most outstanding. While the clinical diagnosis of acute coronary occlusion was well recognized by internists and cardiologists by the beginning of the year 1933, the next five years were characterized by a better appreciation of the clinical diagnosis of this condition by the mass of practising physicians. Time is required for the leaven to work. There is always a lag between discovery and popular acceptance.

Furthermore, during these five years many advances were made in the diagnosis of this condition, notably in the use of precordial leads and better recognition of atypical cases. Contrariwise, there was also considerable improvement in the differentiation of acute coronary occlusion from other conditions. This tends to reduce the number of deaths attributed to this cause. With regard to improvements in electrocardiographic diagnosis, it should be borne in mind that most fatal cases are diagnosed on the basis of the clinical picture, and without the aid of this valuable diagnostic adjunct.

Granting that improvement in diagnosis is the major factor responsible for the increase in reported mortality, is it the only factor? Among regularly admitted patients to 26 civilian hospitals approved for internship by the American Medical Association, deaths attributed to acute coronary occlusion increased 70 per cent during these five years, while admissions for all causes increased 9.5 per cent. In a group of 11 selected hospitals, most of which are teaching institutions and whose staffs have been especially interested in this problem, the number of deaths attributed to this disease increased 60 per cent in 1937 over 1933. Can it be stated with justification that the diagnostic acumen of the staffs of these hospitals increased to that extent in so short a period? It is difficult to escape the impression that the increase in reported mortality from acute coronary occlusion may have been in part due to a certain actual increase in this disease.

It is doubtful if the increase in deaths from this cause can be attributed to any great extent to greater interest in this problem, as a result of which more patients were admitted to hospitals. Of the deaths attributed to acute

coronary occlusion in 1933, 17 per cent occurred in hospitals, while in 1937 only 12.8 per cent occurred among regularly admitted patients to hospitals approved for internship by the American Medical Association.

Furthermore, there was an increase of 135 per cent in the reported mortality from all sources among white persons as compared with only 22 per cent among colored persons during these five years. There was an increase of 78 per cent in the number of deaths, attributed to this cause among white persons in hospitals approved for internship by the American Medical Association, but no increase among Negroes. In hospitals especially both races were subjected to the same diagnostic standards. If improvement in diagnosis were the only factor, the *percentage increase* should have been approximately the same for the two races. Since this did not prevail, it seems likely that a part of this increase may actually have been due to more deaths from this disease among white persons.

SUMMARY

During the 5-year period between January 1, 1933 and December 31, 1937, there were 5116 deaths reported as due to acute coronary occlusion and other nearly synonymous diagnostic terms in Philadelphia. The age distribution of these deaths corresponded quite closely to that of cases in which the diagnoses were based on necropsy findings. Despite an increase of 126 per cent in the number of deaths reported as due to this cause during this period, the age distribution and mean ages at death were nearly the same in each of the five years under study.

Acute coronary occlusion is not primarily a problem of the aged. Only 24.5 per cent of deaths reported as due to this cause occurred among persons past 70 years of age. The peak incidence, 32.9 per cent, occurred in the 60-69 year age period. Of the total deaths attributed to this cause 41.9 per cent occurred among persons younger than 60 years of age. In the 50-59 year age period, acute coronary occlusion was the cause of 26.0 per cent of all deaths reported as due to heart disease. With each succeeding decade this condition accounts for a smaller percentage of the total heart disease mortality. Only 5.5 per cent of deaths from heart disease among persons past 80 years of age were attributed to acute coronary occlusion.

The mean age at death was 61.2 years. The mean ages and age distribution indicated deaths at younger ages among coroner's cases and somewhat older ages among deaths occurring in the homes. The mean ages at death among males was younger by more than four years than among females. Although the mortality rates indicated relatively fewer deaths among Negroes, the mean age at death among colored persons was younger by several years than among white persons.

The mean annual mortality rate was 53 per 100,000 white persons; 76 per 100,000 white males, but only 37 per 100,000 white females. The mean

annual mortality rate was 21 per 100,000 colored persons; 23 per 100,000 colored males and 19 per 100,000 females. The mortality rate among white persons increased from 36 per 100,000 in 1933 to 84 per 100,000 in 1937. Among Negroes it only increased from 25 per 100,000 in 1933 to 28 per 100,000 in 1937. In some of the intervening years it was even lower than these figures among Negroes.

The monthly incidence of deaths indicates considerably more deaths from this cause during the colder months than in the summer.

Based on estimated mortality rates, professional men appeared to be more likely to die from this cause than other occupational groups, especially workers. Since it is not known whether the diagnoses of acute coronary occlusion are made with equal accuracy among persons in various occupational groups at the present time, caution is suggested in interpreting the higher reported mortality among professional men too literally.

The increased reported mortality from acute coronary occlusion of 126 per cent in five years could not be accounted for to any great extent by more deaths among the aged reported as due to this cause, by an aging of the population in general or the foreign born population in particular, or by changes in diagnostic terminology. Improvement in diagnosis appeared to be the most important factor responsible for the increase in reported mortality. Doubt is expressed whether an increase of 70 per cent in deaths attributed to this cause in 26 civilian hospitals approved for internship by the American Medical Association or an increase of 60 per cent in 11 selected hospitals during these few years can be *entirely* explained on the basis of improvements in diagnosis.

Deaths reported as due to acute coronary occlusion among white persons regularly admitted to hospitals approved by the American Medical Association increased 78 per cent, while there was no increase in deaths from this cause among colored patients. Since both races are subjected to the same diagnostic standards, the *percentage increase* should have been about the same if better diagnoses were the only factor. The possibility of a certain degree of actual increase in mortality from acute coronary occlusion should not be dismissed summarily.

REFERENCES

1. HERRICK, J. B.: Clinical features of sudden obstruction of the coronary arteries, Jr. Am. Med. Assoc., 1912, lix, 2015.
2. CUSHING, HARVEY: Life of Sir William Osler, Oxford, Clarendon Press, 1925. Vol. 11, page 604.
3. HERRICK, J. B.: Thrombosis of the coronary arteries, Jr. Am. Med. Assoc., 1919, lxxii, 387.
4. HEDLEY, O. F.: Mortality from rheumatic heart disease in Philadelphia during 1936, Pub. Health Rep., 1937, lii, 1907.
5. LEVINE, S. A.: Coronary thrombosis: its various clinical features, 1929, Williams and Wilkins, Baltimore. Medicine monographs Vol. XVI.

6. SAPHIR, O., PRIEST, W. S., HAMBURGER, W. W., and KATZ, LOUIS N.: Coronary arteriosclerosis, coronary thrombosis, and resulting myocardial changes, *Am. Heart Jr.*, 1935, x, 567 and 762.
7. APPLEBAUM, EMANUEL, and NICOLSON, GERTRUDE H. B.: Occlusion diseases of the coronary arteries—an analysis of 168 cases, with electrocardiographic correlation in 36 of these, *Am. Heart Jr.*, 1935, x, 662.
8. MEAKINS, J. C., and EAKIN, W. W.: Coronary thrombosis: a clinical and pathological study, *Canad. Med. Assoc. Jr.*, 1932, xxvi, 18.
9. HEDLEY, O. F.: An analysis of 5116 deaths reported as due to acute coronary occlusion in Philadelphia from January 1, 1933 to December 31, 1937, *Pub. Health Rep.*, 1939, liv, 972.

OBSERVATIONS UPON THE EXPERIMENTAL AND CLINICAL USE OF SULFAPYRIDINE. III. THE MECHANISM OF RECOVERY FROM PNEUMOCOCCAL PNEUMONIA IN PATIENTS TREATED WITH SULFAPYRIDINE *

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It has been established by a number of investigators^{1, 2, 3, 4, 5} that sulfapyridine exercises a bacteriostatic effect upon pneumococci in vitro. Fleming¹ has shown that the growth of pneumococci in human whole blood is inhibited by sulfapyridine, but that in the absence of leukocytes the organisms are not destroyed. When leukocytes are present in the blood-sulfapyridine preparations, the growth of pneumococci is not only inhibited, but in many instances the blood is rendered sterile, probably as a result of the combined action of the sulfapyridine and the natural antibacterial substances in the serum. If type-specific pneumococcal antiserum is added to similar preparations, this sterilizing effect is greatly enhanced.

Likewise in vivo the action of sulfapyridine seems to be principally bacteriostatic. We⁶ have studied the effect of sulfapyridine therapy upon the evolution of experimental pneumococcal peritonitis in mice, and have noted that the drug inhibits the multiplication of pneumococci in the peritoneal cavity. However, very little phagocytosis has been noted in the peritoneal exudates, and unless therapy with sulfapyridine is maintained for several days, the organisms resume active multiplication as soon as treatment is discontinued. When, on the other hand, the mice are treated with a small amount of antipneumococcal serum during the phase of bacteriostasis, the pneumococci become opsonized and are quickly destroyed by phagocytosis.

These facts suggest that type-specific antibodies play an important rôle in the process of recovery from pneumococcal pneumonia following treatment with sulfapyridine. Since no study of the antibodies in the serum of patients ill with pneumococcal pneumonia and treated with sulfapyridine has been reported, it is thought advisable to present certain data bearing upon this point.

METHODS

The antibody content of the serum of 12 patients ill with lobar pneumonia caused by pneumococci of types I, II or III was followed during the course of sulfapyridine therapy. Specimens of blood serum were obtained

* Received for publication July 1, 1939.

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This investigation was supported by a grant from The Chemical Foundation, Inc., of New York City.

just prior to the start of treatment with sulfapyridine and then at two day intervals until the patients left the hospital. The antibody content of these specimens of serum was subsequently determined by mouse-protection tests. A pure bred strain of mice (C. F. 1) was used in all experiments. Each mouse was injected intraperitoneally with 0.5 c.c. of varying dilutions of a 14 hour rabbit's blood broth culture of pneumococci immediately after having received by the same route 0.5 c.c. of a 1 to 5 dilution of the serum to be tested. The culture dilutions varied logarithmically from 1:5 to 1:50,000,000. Five mice were injected with each dilution of culture. The pneumococci of types I, II and III used in these tests were cultured only after several mouse passages and were all highly virulent, 10^{-8} c.c. of a 14 hour culture killing control mice regularly in 20 hours. Each test was terminated after 96 hours, and all mice living at the end of this time were counted as survivals. The final results were calculated in terms of antibody units * per c.c. of the patient's serum.

RESULTS

The results of the antibody studies are summarized in table 1. The day of essential recovery is taken as that day upon which the rectal temperature became essentially normal (below 99° F.) and after which the patient's course in the hospital progressed uneventfully.

It will be noted that essential recovery from the pneumonia occurred in seven of the 12 cases before specific antibody could be detected in the serum. In chart 1 the graphic record of such a case is presented which shows that although essential recovery occurred on the fifth day of disease (and the third day of treatment) antibody could not be detected in the patient's serum until the seventh day. No antibody was found at any time in the serum of the one patient in the group who failed to recover. Also one patient who recovered promptly from type I pneumonia showed no antibody in the blood serum even 16 days after the onset of his illness. No later specimens of serum were examined.

COMMENT

The results of these studies in patients ill with pneumococcal pneumonia treated with sulfapyridine are in agreement with similar observations made by McIntosh and Whitby⁵ in experimental pneumococcal infections. They found that mice infected with pneumococci and treated with sulfapyridine developed a type specific immunity to the organism causing the infection. The time of appearance and titre of antibody in the serum of the treated animals was observed to be approximately the same as that found in the untreated mice immunized with doses of killed pneumococci calculated to be comparable to the immunizing dose of living cocci in the treated animals. Thus, it appeared that the immune response of the mice was in no way altered

* 1 unit = The amount of antibody which protects against 1,000,000 lethal doses of pneumococcus.

TABLE I

The Appearance of Type Specific Pneumococcal Antibody in the Sera of Patients Ill with Lobar Pneumonia and Treated with Sulfapyridine

Pa- tient's Hosp. No.	Type of Pneu- mococ- cus	Time of Development and Titer of Antibodies (Day of Disease—units per c.c.)															
		2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
160955	I			0	*	10 ⁻⁴		10		10		10					
160947	"	0		0		10 ⁻⁴		10 ⁻³		10 ⁻¹							
160964	"				0		0	*	10		10						
161304	"					0	*	0		0		0		0		0	
165765	"		0		*	10 ⁻⁵		10 ⁻³									
162439	"			0			*		10 ⁻³			10 ⁻¹					
164268	II		0		0		10 ⁻¹		10 ⁻¹		10 ⁻¹		10 ⁻¹		10+		10+
165533	"		0		*												
165784	"				0		10 ⁻⁴		1		1		1				
160992	III			0	0	0	0			0	0	Died					
160993	"			0			*	0		10 ⁻¹		10 ⁻¹					
165521	"		0		*		0		0	10 ⁻⁴		10 ⁻⁴		10 ⁻⁴			

* Day of essential recovery.

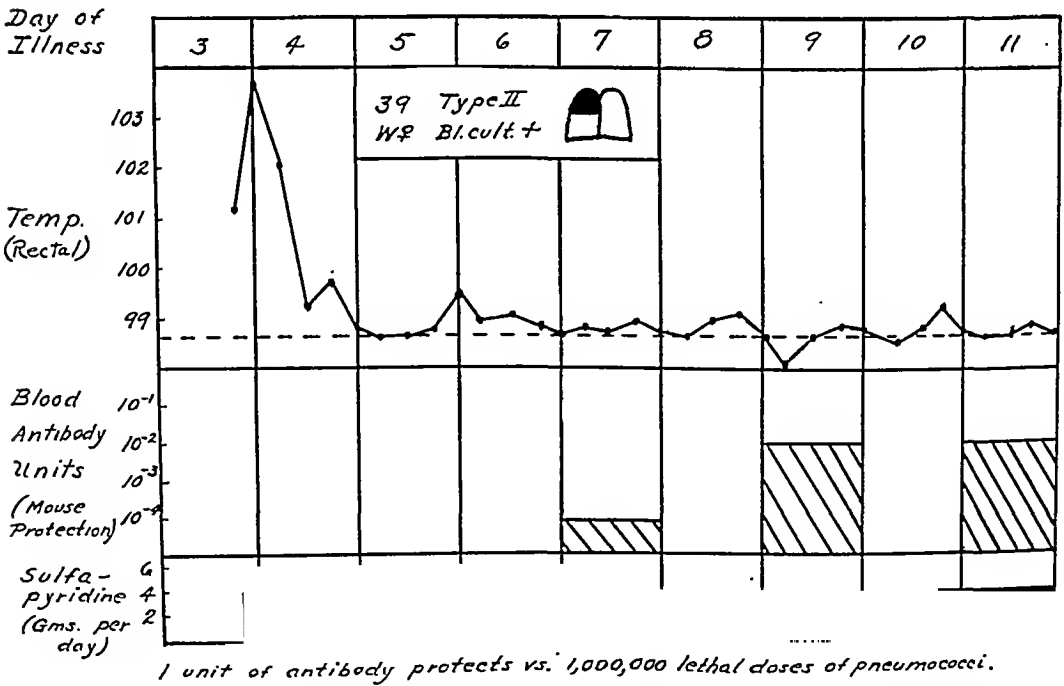


CHART I. Blood antibodies (mouse protective) in pneumococcic pneumonia treated with sulfapyridine.

by sulfapyridine treatment. Likewise, it may be concluded from the present study that the antibody response of patients with pneumonia treated with sulfapyridine is much the same as that observed in untreated patients during the natural course of the disease.

The fact that antibodies may not appear in the serum until several days after fever has subsided suggests a possible explanation for the frequent relapses suffered by patients with pneumonia who have been treated sparingly with sulfapyridine. In their first series of patients treated with the drug, Evans and Gaisford⁷ observed on several occasions, secondary pyrexia following early withdrawal of therapy. In certain of these cases the secondary rise in temperature was associated with a spread of the pneumonia. Dreosti⁸ treated 100 patients with sulfapyridine, stopping the drug after two to four days of normal temperature; 10 per cent of them suffered relapses. Alsted⁹ has recently described six cases of type III pneumonia in which the initial response to treatment with sulfapyridine was satisfactory. Five relapses occurred among the six cases, four of the patients requiring additional therapy. In a previous publication we¹⁰ have reported two comparable cases of relapse due to inadequate treatment with sulfapyridine.

As already mentioned, sulfapyridine seems to act only as a bacteriostatic agent in pneumococcal infections. Its primary effect in pneumonia is probably to hold in check the pneumococcal infection in the lung. There is adequate experimental evidence favoring the view that the eventual destruction of pneumococci within the lung, and thus the final recovery from pneumococcal pneumonia, depends upon phagocytosis. Since encapsulated pneumococci are known to be resistant to phagocytosis unless opsonized by specific antibody, it is only logical to conclude that type specific antibodies play an important part in the process of final recovery. If, in any given case of pneumonia, a bacteriostatic agent such as sulfapyridine is withdrawn before sufficient antibodies have developed to promote phagocytosis,* a relapse of the pneumonia is likely to ensue. A normal temperature does not necessarily indicate complete recovery.

Relapses may be avoided by continuing sulfapyridine treatment over a sufficiently long period of time.¹⁰ If toxic reactions to the drug necessitate an early withdrawal of therapy, it would seem advisable to treat the patient with antipneumococcal serum unless immunological tests have revealed the presence of an excess of antibody in the blood. We have found the skin test with type-specific capsular polysaccharide,^{12, 13, 14} a valuable index of antibody in such cases. The skin test may also be used routinely as a guide to sulfapyridine therapy, for if it is performed at daily intervals, treatment may be safely discontinued in uncomplicated cases of pneumonia as soon as the test becomes positive. It should be pointed out, however, that a positive skin test is occasionally observed in certain cases complicated by pneumococ-

* It is possible that sufficient immune bodies may accumulate locally in the lung before an excess can be detected in the blood.¹¹ Thus an absence of circulating antibody does not necessarily indicate that a relapse must invariably occur if treatment is discontinued. (See fourth case in table 1.)

cal empyema, meningitis, and endocarditis¹⁴ where further chemotherapy is usually indicated. By the use of the skin test with type-specific capsular polysaccharide it may be possible to shorten the required period of chemotherapy to a minimum, thus decreasing the chance of toxic reactions to the drug without subjecting the patient to the risk of suffering a relapse.

Finally it is a fact of considerable theoretical significance that under sulfapyridine treatment the fever may be controlled several days before antibodies are detected in the blood. In the average untreated case of pneumococcal pneumonia antibodies appear in the serum at approximately the time of natural crisis.^{15, 16, 17} Therefore, it cannot be maintained that the abrupt fall in temperature usually effected by adequate sulfapyridine therapy is due necessarily to a coincidental natural crisis. The drop in temperature must in the majority of cases be attributed to the direct action of the drug.

SUMMARY

1. Type-specific antibodies often do not appear in the blood serum of patients ill with pneumococcal pneumonia and treated with sulfapyridine until several days after the temperature has fallen to normal.

2. Evidence is presented that type-specific antibodies play an important rôle in the process of recovery from pneumococcal pneumonia following treatment with sulfapyridine.

3. The lateness of the appearance of circulating antibodies is offered as a possible explanation for the relapses which frequently occur when sulfapyridine therapy is discontinued too soon.

BIBLIOGRAPHY

1. FLEMING, A.: The antibacterial action in vitro of 2(p-aminobenzenesulphonamido) pyridine on pneumococci and streptococci, *Lancet*, 1938, ii, 74.
2. BLISS, E. A., and LONG, P. H.: Comparison of bacteriostatic effects of sulfanilamide and sulfapyridine (2 sulfanilyl aminopyridine) on bacteria in broth cultures, *Proc. Soc. Exper. Biol. and Med.*, 1938, xxxix, 483.
3. LONG, P. H., BLISS, E. A., and FEINSTONE, W. H.: The effect of sulfapyridine, sulfanilamide and related compounds in bacterial infections, *Pennsylvania Med. Jr.*, 1939, xlii, 483.
4. LONG, P. H., and BLISS, E. A.: The relation of strain resistance to the chemotherapeutic effects of sulfapyridine in experimental infections in mice, *ANN. INT. MED.*, 1939, xiii, 232.
5. MCINTOSH, J., and WHITBY, L. E. H.: The mode of action of the drugs of the sulphonamide group, *Lancet*, 1939, i, 413.
6. LONG, P. H.: Unpublished observations.
7. EVANS, G. M., and GAISFORD, W. F.: Treatment of pneumonia with 2(p-aminobenzene-sulphonamido) pyridine, *Lancet*, 1938, ii, 14.
8. AGRANAT, A. L., DREOSTI, A. O., and ORDMAN, D.: Treatment of pneumonia with 2(p-aminobenzenesulphonamido) pyridine (M. & B. 693), *Lancet*, 1939, i, 309.
9. ALSTED, G.: Type III pneumococcal pneumonia, effect of M. & B. 693, *Lancet*, 1939, i, 869.
10. LONG, P. H., and WOOD, W. B.: The treatment of pneumococcal pneumonia with sulfapyridine, *ANN. INT. MED.*, 1939, xxiii, 487-529.

11. ROBERTSON, O. H., GRAESER, J. B., COGGESHALL, L. T., and HARRISON, M. A.: Relation of circulating antipneumococcal immune substances to the course of lobar pneumonia. II. Acquired immune substances, *Jr. Clin. Invest.*, 1934, xiii, 633.
12. FRANCIS, T.: The value of the skin test with type-specific capsular polysaccharide in the serum treatment of type I pneumococcus pneumonia, *Jr. Exper. Med.*, 1933, lvii, 617.
13. MACLEOD, C. M., HOAGLAND, C. L., and BEESON, P. B.: The use of the skin test with type-specific polysaccharide in the control of serum dosage in pneumococcal pneumonia, *Jr. Clin. Invest.*, 1938, xvii, 739.
14. WOOD, W. B.: The control of the dosage of antiserum in the treatment of pneumococcal pneumonia. I. A study of the mechanism of the skin reaction to type-specific polysaccharide. II. The clinical application of Dr. Francis' skin test. To be published.
15. SIA, R. H. P., ROBERTSON, O. H., WOO, S. T., and CHEER, S. N.: The occurrence of antipneumococcus substances in the blood serum in lobar pneumonia, *Proc. Soc. Exper. Biol. and Med.*, 1925, xxii, 406.
16. LORD, F. T., and NESCHE, G. E.: Antibody and agglutinin in pneumococcus pneumonia, *Jr. Exper. Med.*, 1929, 1, 449.
17. LANGLEY, G. J., MACHAY, W., and STANT, L.: Studies in pneumonia with special reference to agglutinins, *Quart. Jr. Med.*, 1936, v, 251.

OBSERVATIONS ON TOXICITY AND CLINICAL VALUE OF STROPHANTHIN *

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THE efficacy of strophanthin in cardiac failure was studied carefully in a large series of patients by Fraenkel ⁷ in 1906 and by Vaquez ²³ in 1909. Their enthusiastic reports stimulated great interest in the therapeutic possibilities of this drug with the result that numerous observers soon corroborated their favorable results. The scope of this report is too limited to permit a complete survey of the very extensive literature on this subject, but the excellent monograph of Fraenkel ⁸ will be found to contain a critical digest of practically all work done on the pharmacological and clinical aspects of strophanthin. It can be stated, however, that the available literature is almost exclusively favorable so that the use of strophanthin has now become an established procedure in Europe, particularly in France and Germany. The widespread acceptance of this drug abroad is in striking contrast to the reluctance which physicians in this country still display to the use of strophanthin in cardiac failure. Such hesitancy is based chiefly on the opinion that strophanthin is dangerous, that it can be given only by intravenous injection and that digitalis given orally can produce all the beneficial effects claimed for strophanthin without the attendant dangers. This striking divergence of opinion prompted us to re-investigate the problem, particularly with reference to toxicity, electrocardiographic changes and clinical effects in normal persons and in patients with cardiac failure in order to compare our results with those of foreign observers.

It is generally accepted that the pharmacological properties of strophanthin and digitalis are practically identical except that the former acts more promptly and is eliminated with greater speed (Fraenkel,^{8, 9} Lendle,^{17, 18} Wallace and Van Dyke,²⁴ Weese²⁵). The faster elimination or destruction of strophanthin is an important factor in reducing its cumulative action and toxicity after repeated injections. The clinical and electrocardiographic manifestations of strophanthin toxicity are also the same as those of digitalis, although Aschenbrenner¹ states that therapeutic doses of strophanthin are less likely to produce changes in the ST segment of the electrocardiogram than comparable doses of digitalis. Such comparisons should not, however, tempt the physician to use strophanthin in doses larger than those in the therapeutic range. Gold, Hitzig, Gelfand, and Glassman¹¹ found that a given toxic dose of digitalis did not always produce constant effects, even in the same patient. They also observed that a better response

* Received for publication October 31, 1938.

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Aided by a grant from the A. B. Kuppenheimer Fund.

could sometimes be obtained from the same dose after a suitable rest period. We have observed similar variations in response and have noted frequently that patients will react better to digitalis after edema or effusions are removed. Eckey⁶ reports patients who are hypersensitive to strophanthin since they showed toxic effects after 0.3 mg. of strophanthin given daily for two days. Caution is advised by Dieckhoff and Schulze⁴ in diphtheria because they found the cat's heart to be hypersensitive to digitalis and strophanthin if previously injured with diphtheria toxin. A number of suggestions have been offered by which toxic effects of strophanthin might be decreased. Bischoff^{2,3} suggested the addition of 0.1 or 0.2 gm. of caffeine sodium benzoate to the strophanthin in order to reduce the toxicity of the latter. The method has not been accepted generally and its value is questioned by several observers. Rothberger and Zwillinger²¹ observed that magnesium sulphate could restore normal rhythm in animals poisoned by strophanthin provided ventricular fibrillation was not present. Zwillinger^{29,30} found magnesium sulphate effective in man when given intravenously for extra-systoles and heart block caused by strophanthin. Fraenkel⁸ and others have found strophanthin K somewhat less toxic than ouabain, and about 30 per cent less toxic than strophanthin G. This greater safety and the fact that strophanthin K is more soluble in water than the other preparations are the chief reasons for preferring this preparation, although the others also produce excellent results.

Extensive experience by a number of observers over many years has shown that strophanthin is no more dangerous than digitalis if used in proper dosage and in suitable patients. Practically all untoward results in the past were due to dosage which was far too great or administration of strophanthin in patients who had received large doses of digitalis or who showed definite evidence of previous digitalization. Grünbaum¹² has given over 10,000 injections of strophanthin during the past 10 years without observing a single death directly attributable to the drug and Fraenkel with a larger experience is equally convinced of the safety of strophanthin if given in the proper manner. It is well to remember that the average maximum initial daily dose, 0.5 mg. of strophanthin, is equal to the effect of approximately 300 mg., or less than 5 grains, of digitalis. Such a dose of strophanthin is usually sufficient for the first 24 hours, but the total digitalis equivalent is still low even if an additional smaller dose of strophanthin is required in very severe cases. It should be mentioned in passing that failure was encountered in patients in whom neither strophanthin nor other cardiac remedies were indicated, such as in tachycardia of thyrotoxicosis, various arrhythmias, heart lesions not associated with cardiac failure, acute infectious myocarditis and in moribund patients.

The fact that strophanthin can be administered only by intravenous injection should not preclude its use in patients where the intravenous route is preferable to oral administration or when the former method is the only one practicable. Weese²⁵ pointed out that intravenous injection of stro-

phanthin permitted rapid administration of an exact dose capable of an early and intense effect. There is thus no necessity for doses approaching toxic limits when rapid effectiveness is desirable and where cumulative action is undesirable. Intravenous administration is also of value in the presence of congestion of the liver or of the gastrointestinal tract where absorption of oral medication may be greatly delayed. Fraenkel and Thauer¹⁰ observed that hepatic congestion interfered with the efficacy of digitalis administered orally and believed the cause to be stagnation of large amounts of blood in the liver with the result that a greater part of the orally ingested digitalis is retained by that organ leaving less for transport to and fixation by the heart. It is no simple matter to estimate the exact dose of digitalis necessary for a full effect when given orally. Weese does not believe that one can compute the required dose for full digitalization by using the weight of the patient as a guide. He believes that other factors are operative, such as the reserve still inherent in the heart, the degree and type of heart failure, its underlying cause, and the uncertainty of absorption from the gastrointestinal tract in the presence of passive congestion. To these may be added the presence or absence of auricular fibrillation, the weight of retained water in edema, and the amount of excess fat in obese patients.

Weese²⁶ showed that slow intravenous injection exposes the heart for a longer period to the strophanthin contained in the blood with the result that a greater proportion of the given total dose is taken up by the heart. This is the reason for advocating very slow administration, even diluting the preparation with 10 to 20 c.c. of 10 per cent dextrose solution. This author^{26, 25, 27} and Lendle¹⁶ found that about 9 per cent of the minimum lethal dose of strophanthin is fixed to the heart after intravenous injection, the remainder being taken up by the skeletal muscles, liver and kidneys. The lungs and blood do not take up appreciable quantities of the drug, a point of importance in calculating dosage by intravenous injections. Weese also showed that as much as an entire minimum lethal dose is absorbed by the heart and other tissues in one circulatory cycle, thus showing the rapidity with which strophanthin is absorbed after intravenous injection. The real advantages of strophanthin are, however, rapidity of absorption and of effect, exactness of dosage, a fairly accurate idea of how much of an injected dose will be fixed to the heart, and the avoidance of uncertainty in absorption in the presence of venous stasis in the liver or gastrointestinal tract (Herzog¹⁴ and Fraenkel⁸). These advantages, rather than properties not possessed by digitalis form the basis for the choice of strophanthin in certain instances of cardiac failure.

The many reports of excellent clinical results with strophanthin are particularly impressive when it is remembered that many of the patients suffered from cardiac failure with regular rhythm; the underlying basis being coronary sclerosis or hypertension. Vaquez,²³ Fraenkel,⁸ Edens,⁵ Zak,²⁸ Zimmermann-Meinzingen and Jagic¹⁵ reported success with intravenous injection of strophanthin in patients who failed to respond to digi-

talis administered orally. Fraenkel recommends strophanthin in cardiac failure of any variety and points out that it is the failure and not its cause which requires the drug. Strophanthin is stated to be very effective in comparison with digitalis in acute cardiac emergencies such as cardiac asthma or abrupt congestive failure of mitral disease where the dosage must be exact and where absorption from the congested gastrointestinal tract is uncertain. Oral digitalis even in very large doses does not act for about two hours, an interval obviously too long in such cardiac emergencies. Fraenkel states that cardiac failure in hypertension is one of the special fields where strophanthin shows its superiority over digitalis. This is of importance since it is well known that digitalis orally may fail in such patients.

METHOD AND RESULTS

We decided to use the utmost caution in our experiments and at first disregarded statements in the literature that strophanthin was safe when used in the manner previously described. We took advantage of the well known pharmacological fact that strophanthin and digitalis in therapeutic doses produce practically no manifestations in normal persons. A solution of strophanthin K was used, 1 c.c. of which corresponded to 0.25 mg. of strophanthin activity according to U. S. P. XI specifications.* The preparation was put up in hard glass rubber-stoppered bottles and no appreciable deterioration could be ascertained one year after being placed in such containers in accordance with the suggestions of R. L. Levy and G. E. Cullen.¹⁹ The intravenous injections were given slowly, no less than 20 seconds being consumed with an undiluted solution and a longer period when diluted in dextrose solution. All patients were observed for nausea, vomiting, precordial oppression, arrhythmia and other signs of toxicity. Electrocardiograms were made before injections and at varying intervals after administration.

The first group to be studied consisted of nine normal persons without history or evidence of cardiac disease. All were kept in bed and a control electrocardiogram consisting of the three standard leads was made before administration of the drug. Strophanthin 0.5 mg. was then injected intravenously and electrocardiograms were made at intervals of five, 15, 30, 60 minutes, two hours and 24 hours after injection. We disregarded minimal changes in amplitude, that is, of 1 mm. or less, because one of us had observed previously that such slight changes can occur without apparent cause. None of these patients showed clinical evidence of toxicity. The electrocardiogram after injection showed moderate slowing of the heart rate in three instances, beginning in five minutes and disappearing after two hours. The T-wave became inverted only once, the change being seen only in Lead III. These results convinced us that 0.5 mg. was a safe dose and

* The Abbott Laboratories furnished us with the supply of strophanthin K and at our request assayed its potency from time to time.

prompted us to study the effects of 0.75 mg. in four normal persons in a similar manner. No clinical or electrocardiographic evidence of toxicity was observed after this dose, an amount distinctly above the ordinary maximum used during the first 24 hours.

We then studied the effects of continuous use of strophanthin in 13 patients with cardiac failure, 11 of whom had hypertensive cardiac insufficiency with regular rhythm, and two with failure from old rheumatic heart disease with auricular fibrillation. All patients were severely decompensated as evidenced by marked dyspnea and orthopnea, extensive edema, marked congestion of the lungs and liver, and engorged cervical veins. A control period of from three to five days was maintained during which the patients were kept at absolute bed rest except for daily weighing. Control electrocardiograms were taken in the usual manner, including precordial leads, the total fluid intake was limited to 1200 c.c. daily, the urine output for 24 hours was measured, and a soft diet without salt restriction was used in all instances. Placeboes were given to all patients during this period and small doses of morphine or barbiturates were used only when absolutely necessary. No drugs acting directly on the cardiovascular system were employed during this time. Daily observations were made of the pulse rate, body weight, urine output, degree of dyspnea, nocturnal dyspnea and orthopnea, extent of edema, evidences of pulmonary and hepatic congestion, degree of sweating and other subjective symptoms. Similar observations were made after strophanthin therapy was instituted, the electrocardiograms being taken daily 20 minutes after each injection. The initial daily dose of strophanthin was usually 0.5 mg. either as a single dose or as two injections of 0.25 mg. given at an interval of 12 hours. Occasionally only one dose of 0.3 mg. was given during the first day. Subsequent treatment consisted of daily injections of 0.3 mg. together with accessory medication when necessary. Such accessory treatment consisted of small doses of morphine at night in three instances and a mercurial diuretic in four patients.

There was marked clinical improvement in every instance. Many of the patients volunteered the information that they could breathe easier and felt definitely better shortly after the first injection of strophanthin. Some of the patients actually went to sleep about one hour after the drug was administered. The majority could sleep without the aid of hypnotics or sedatives and paroxysmal nocturnal dyspnea no longer occurred. We have already mentioned that sweating became greatly increased in some instances after strophanthin, the patients stating that their bedclothes were actually drenched during the night. We also observed at times that the loss in body weight was sometimes marked when the urinary output was not greatly increased, a change attributed to increased extrarenal water loss. Daily electrocardiograms showed no significant changes except one instance in which transient prolongation of the PR interval from 0.16 to 0.22 second occurred. This change disappeared during the next day in spite of the fact that the same dosage of strophanthin was maintained. The T-wave in

Lead III or IV became changed in direction as compared with the control in three instances, but no further electrocardiographic changes were noted in spite of continued use of strophanthin in the same dosage. None of the patients presented clinical evidence of strophanthin toxicity. Four of the patients with severe hypertensive failure who had been on previous management with digitalis therapy with moderate or no benefit showed a striking response to strophanthin.

The following case reports will illustrate the course of some of these patients:

CASE REPORTS

Case 1. E. W., male, aged 63, colored, entered the Michael Reese Hospital on February 17, 1938. Dyspnea had been present for the past two years and was becoming rapidly worse. Dull substernal pain and pain in the left shoulder were present. His dyspnea was practically constant. There had been marked progressive edema of the ankles especially in the preceding four days. Cough with blood-tinged sputum had been present for some time and headache and vertigo had become prominent during the past few weeks. He had had typhoid fever in 1907, "rheumatism" as a child, and gonorrhea and chancre 25 years previously with practically no treatment. The essential findings on examination were: Extreme dyspnea and orthopnea, engorged pulsating cervical veins, inspiratory and expiratory wheezing and sonorous râles diffusely and crepitant râles in both bases of the lungs posteriorly. The apex beat was palpable in the sixth interspace, to the left of the midclavicular line. The heart tones were distant and an occasional extra-systole was heard. The abdomen was tense and distended, the liver edge being palpable six fingers-breadth below the costal margin. Shifting dullness in the flanks and a fluid wave could be elicited. The scrotum was markedly edematous and extensive edema was present in both lower extremities. The blood pressure was 240 mm. of mercury systolic and 130 diastolic. A teleoroentgenogram showed enlargement of the right auricle and left ventricle with a cardiothoracic ratio of 18-31. Fluid was seen at both bases and the hilus markings were denser than normal. The blood chemical and serological tests were normal. The patient was observed for eight days under control conditions, being at absolute bed rest and receiving small doses of luminal and ephedrin in addition to the experimental measures previously mentioned. Morphine sulphate $\frac{1}{4}$ gr. subcutaneously was administered for extreme restlessness once during this period. His weight during the control period varied from 151 to 154 lbs.; his total fluid intake in 24 hours ranged between 36 and 48 oz., and his urine output between 37 and 47 oz. per day. Strophanthin 0.5 mg. intravenously was then administered. Shortly after the administration of strophanthin the patient remarked that he had not felt so well in a long time and went to sleep. No further sedation was necessary and he slept well every night without the use of sedatives. Perspiration was perceptibly increased; dyspnea and wheezing were definitely reduced; the weight steadily diminished to 135 lbs. 12 days after the first injection of strophanthin, although the intake and urinary output remained unchanged. He received 0.3 mg. of strophanthin daily after the first injection until his discharge, at which time he felt very much improved. He was instructed to take maintenance doses of digitalis while at home in order to hold the improvement acquired during his hospital stay. The only electrocardiographic change observed was a reversal of the T-wave in Lead IV, but no further change occurred on continued use of strophanthin.

Case 2. H. M., male, aged 56, entered the Michael Reese Hospital on March 26, 1938. He had been treated in the cardiac clinic with digitalis for four years. His symptoms began in 1934 with congestive failure for which he was hospitalized for

one week. There had been increasing dyspnea on exertion since that time and paroxysmal nocturnal dyspnea became more frequent. Edema of the legs was progressive and reached a marked degree at the time of admission. There was nothing of importance in the past history. Examination revealed an obese individual with orthopnea, engorged cervical veins and enlargement of cardiac dullness to the left and right. The apex beat was palpable in the left anterior axillary line, the heart tones were distant and regular, and a soft systolic murmur was present at the apex. The abdomen was difficult to palpate because of obesity but the liver region was distinctly tender. There was marked pitting edema of the lower extremities. The blood pressure was 190 systolic and 120 diastolic. A teleoroentgenogram of the heart showed the apex to be in the axillary line with a cardiothoracic ratio of 20-29.5 and marked passive congestion of the lungs was obvious. The specific gravity of the urine was 1.012 with an excessive amount of albumin on entrance but only a trace four days after treatment. The red blood count and hemoglobin were normal, the white count was 12,000 and the Wassermann and Kahn reactions of the blood negative. The patient was observed in the usual manner for a control period of four days during which time he received morphine sulphate $\frac{1}{4}$ gr. on two occasions for severe nocturnal dyspnea and phenobarbital gr. $1\frac{1}{2}$ daily. His weight during this control period varied between 230 and 236 lbs.; his total daily fluid intake varied between 18 and 34 ounces, and his urine output between 10 and 34 ounces. He showed no evidence of improvement during this control period. Strophanthin 0.5 mg. was injected once on the first and again on the second day, and 0.3 mg. were given daily thereafter. The patient stated that his precordial pain was less severe after the strophanthin was given and that he breathed with more comfort. Morphine for nocturnal dyspnea was required only once in the ensuing 20 days. No apparent increase in perspiration could be observed. It was of interest to note that the weight of the patient did not decrease during the first five days of strophanthin therapy and that his urine output was only slightly increased. This was in contrast to the striking subjective improvement. Ammonium chloride gr. 90 per day was given three days after strophanthin therapy was begun and continued throughout. Mercupurin 1 c.c. was injected intravenously on the fifth day of treatment but resulted in no appreciable change in weight or urine output. The weight began to decrease, however, on the third day after mercupurin, at which time the patient lost two lbs. Mercupurin was not repeated for an interval of 18 days but the patient's weight dropped gradually until it fell to 203 lbs. and his urine output rose. The electrocardiogram showed prolongation of the PR from 0.16 second to 0.22 second for one day but returned to normal, although strophanthin was continued as before.

DISCUSSION

A critical survey of the literature and the results of our own studies lead us to conclude that there is a definite place for strophanthin in the treatment of certain types of cardiac failure. Digitalis, orally, is unquestionably the most reliable drug in routine treatment but advantage must sometimes be taken of the quicker action and faster elimination of strophanthin, whose pharmacological properties are identical with those of digitalis. Strophanthin is thus an ideal drug in acute cardiac emergencies such as paroxysmal dyspnea, cardiac asthma, acute pulmonary edema of cardiac origin or abrupt congestive failure. The drug can be used in passive congestion of the liver and gastrointestinal tract due to heart failure when absorption of digitalis is uncertain if administered orally. Excellent results

can be obtained in cardiac failure with regular rhythm when associated with hypertension, and in the occasional case of failure where digitalis has proved unsatisfactory. Intravenous administration under such circumstances is certainly no real drawback nor is strophanthin dangerous if the proper precautions and dosage are used.

Strophanthin, whose action becomes apparent in a few minutes, must not be given to a patient who shows evidence of previous digitalization or who has been on digitalis for some time, since rapid additive effects may occur resulting in toxic manifestations. Weese²⁵ and Fraenkel⁸ believe that patients who have received moderate doses of digitalis may receive 0.15 to 0.2 mg. without danger, provided there are no evidences of marked digitalization such as arrhythmia, conduction disturbances, changes in the ST or T or the usual clinical signs of digitalis excess. The dose of strophanthin may then be slowly increased on subsequent days. It is wise to allow an interval of about five days to elapse before strophanthin is injected in a patient who has been previously well digitalized but there is no danger in administering maintenance doses of digitalis orally after the last dose of strophanthin has been used. The presence of extrasystoles in heart failure is not necessarily a contraindication to strophanthin as the arrhythmia may, at times, disappear when the myocardial circulation is improved. It is advisable, however, to be cautious in such instances by beginning with doses of 0.2 or 0.25 mg. instead of the usual 0.5 mg. We have noted disappearance of incomplete heart block and of inversion of the T-wave in Lead III or IV upon continued daily administration of strophanthin. Strophanthin will not eradicate arrhythmia or tachycardia, nor will this drug be of any value in hypertension or organic heart disease if cardiac failure is absent, nor can one expect strophanthin to produce miracles in moribund patients.

Most authors with large experience in the use of this drug suggest 0.3 mg. intravenously as an initial dose once in 24 hours for patients in moderate failure and 0.5 mg. when failure is severe. Subsequent injections of 0.3 mg. daily will usually suffice to maintain the effects of the drug for as long a period as necessary. Beneficial effects are apparent within a few minutes, particularly if the strophanthin is diluted in 10 to 20 c.c. of 10 per cent dextrose solution in order to provide for slow injection so that the heart can absorb a greater part of the total injected dose. Smaller doses at more frequent intervals have been recommended by Tiemann²² but Meyer²⁰ and others find this method inferior to the one previously described, even if the total dose per day was the same in both procedures.

No toxic effects, either clinically or electrocardiographically, were observed by us after single doses of 0.5 or 0.75 mg. intravenously in normal persons, nor were untoward results observed in patients with severe cardiac failure. Continued daily injections of 0.3 mg. for as long as 24 consecutive days failed to produce significant clinical or electrocardiographic evidence of toxicity. These results lead us to agree with Fraenkel and others that strophanthin is a safe remedy when used in proper dosage and in suitable

patients. The therapeutic effects observed by us were in every way comparable to those seen after adequate digitalization.

The rapid response, often in a few minutes after injection of an ordinary therapeutic dose, is a real advantage. Some of our patients would state voluntarily that breathing was easier shortly after receiving strophanthin and others would drop off to sleep. One could hardly expect such improvement for several hours even if large doses of digitalis were given. A further advantage was the absence of cumulative action after prolonged use and is in accordance with the view of Fraenkel⁸ that the daily maintenance dose of 0.3 mg. is eliminated or destroyed in 24 hours. We noted that several of our patients developed marked perspiration after strophanthin and lost considerable weight even when there was no appreciable increase in urinary output. Edema and evidences of passive congestion receded indicating that water loss cannot be estimated accurately by measurement of urinary output alone and that weighing of the patient is a much better index when this procedure is practicable. Fraenkel⁸ and Heineke¹³ arrived at similar conclusions and stated that extrarenal water loss may sometimes exceed the urinary output.

Accessory measures such as sedation and diuretics are sometimes necessary with strophanthin just as they are with digitalis. It is well known that diuresis is greatly enhanced in cardiac failure if the patient is digitalized for a few days before administration of a mercurial diuretic. No such preliminary treatment is necessary with strophanthin since this drug will have become effective before the mercurial diuretic begins to act. We do not mean, of course, that ammonium chloride or similar substances are unnecessary in those patients in whom the diuretic alone fails to act. We merely point out that strophanthin and the diuretic can be placed in the same syringe and be injected as one dose in those patients who do not require preliminary treatment with ammonium salts. Finally, our studies showed that strophanthin can be used in ambulatory patients and that maintenance doses of digitalis may eventually be substituted or the injections of strophanthin can be given at increasing intervals depending on the condition of the patient.

SUMMARY

1. Single intravenous injections of 0.5 or 0.75 mg. of strophanthin K in normal persons failed to produce significant clinical or electrocardiographic evidence of toxicity.
2. Similar absence of toxicity was noted after 0.3 or 0.5 mg. in patients with severe cardiac failure, the majority of whom also had hypertension and regular rhythm.
3. Continued injection of 0.3 mg. daily for as long as 24 days consecutively also failed to produce clinical or electrocardiographic evidence of toxicity in patients with cardiac failure.

4. Accessory measures such as sedation or diuretics were sometimes necessary as with digitalis.

5. The therapeutic results with strophanthin seemed comparable in every way to those obtained by adequate digitalization when digitalis is given orally.

6. We do not advocate strophanthin instead of digitalis in the routine management of cardiac failure. It is our impression, however, that strophanthin is a safe and rapidly acting drug when used in proper dosage and in suitable patients. Its properties are practically those of digitalis but its speed of action and safety render it an ideal drug in acute cardiac emergencies, in marked congestive failure where oral digitalis is absorbed with some uncertainty and in those instances where one wishes to try another drug when digitalis fails.

BIBLIOGRAPHY

1. ASCHENBRENNER, R.: Vergleichende elektrokardiographische Untersuchungen über die Wirkung von Strophanthin und Digitalis, *Verhandl. d. deutsch. Gesellsch. f. inn. Med.*, 1936, *xlvi*, 347-350.
2. BISCHOFF, L.: Der Strophanthinspritze sollte Coffein zugesetzt werden, *Schweiz. med. Wchnschr.*, 1937, *lxvii*, 316.
3. BISCHOFF, L.: Die Strophanthin-Koffeinspritze in die Praxis, *Verhandl. d. deutsch. Gesellsch. f. Kreislaufforsch.*, 1931, 61-63.
4. DIECKHOFF, J., and SCHULZE, E.: Die Empfindlichkeit des diphtherietoxingeschädigten Katzenherzens gegen Digitoxin und Strophanthin, *Arch. f. exper. Path. u. Pharmakol.*, 1936, *clxxxiii*, 561-566.
5. EDENS, E.: Die Strophanthinbehandlung der Angina pectoris, *München. med. Wchnschr.*, 1934, *lxxxi*, 1424-1427.
6. ECKEY, P.: Über einige ungewöhnliche Wirkungen kleiner Strophanthingaben auf die Reizbildung, Reizleitung im Herzen, gleichzeitig ein Beitrag zur Frage der Parasympole, *Deutsch. Arch. f. klin. Med.*, 1936, *clxxvi*, 652-662.
7. FRAENKEL, A.: Zur Digitalistherapie über intravenöse Strophanthintherapie, *Verhandl. d. Kong. f. inn. Med.*, Wiesb., 1906, *xxiii*, 257-266.
8. FRAENKEL, A.: Strophanthintherapie, 1933, J. Springer, Berlin.
9. FRAENKEL, A.: Pharmacological aspect of digitalis therapy, *Lancet*, 1935, *ii*, 1101-1106.
10. FRAENKEL, A., and THAUER, R.: Strophanthintherapie, allgemeine Indikationen und Dosierung, *Klin. Wchnschr.*, 1934, *xiii*, 633-636.
11. GOLD, H., HITZIG, W., GELFAND, B., and GLASSMAN, H.: Qualitative comparisons of various digitalis bodies, *Am. Heart Jr.*, 1930, *vi*, 237-254.
12. GRÜNBAUM, F.: Employment of intravenous strophanthin therapy in chronic heart insufficiency, *Med. Jr. and Rec.*, 1931, *cxxxiv*, 320-324.
13. HEINEKE, A.: Theoretisches und Klinisches zur extrarenalen Ausscheidung cardialer Ödeme, *Deutsch. Arch. f. klin. Med.*, 1919, *cxxx*, 60-94.
14. HERZOG, F.: Über die Gesetze der Digitalis—(Strophanthin-Therapie), *Verhandl. d. deutsch. Gesellsch. f. Kreislaufforsch.*, 1931, 45-50.
15. JAGIC, N., and ZIMMERMANN-MEINZINGEN, O.: Beiträge zur Strophanthintherapie, *München. med. Wchnschr.*, 1936, *lxxxiii*, 1623-1628.
16. LENDLE, L.: Über die Wirkungsbedingungen des Strophanthidine (Verteilung, Elimination und Kumulation) sowie die Wirksamkeit einiger Strophanthidin-Esterverbindungen, *Arch. f. exper. Path. u. Pharmakol.*, 1936, *clxxxii*, 72-86.
17. LENDLE, L.: Über herzwirksame Glycoside; Strophanthinelimination unter verschiedenen Bedingungen, *Arch. f. exper. Path. u. Pharmakol.*, 1933, *clxix*, 392-413.

18. LENDLE, L.: Über die Eliminationsgeschwindigkeit und Kumulationsneigung von Digitalisglykosiden und Strophanthin, Arch. f. exper. Path. u. Pharmacol., 1936, clxxx, 518-538.
19. LEVY, R. L., and CULLEN, G. E.: Deterioration of crystalline strophanthin in aqueous solution, Jr. Exper. Med., 1920, xxxi, 267.
20. MEYER, F.: Normale oder unterschwellige Strophanthin-dosierung? Klin. Wchnschr., 1936, xv, 1238-1241.
21. ROTHBERGER, C. J., and ZWILLINGER, L.: Über die Wirkung von Magnesium auf die Strophanthin- und die Barium-Tachykardie, Arch. f. exper. Path. u. Pharmacol., 1936, clxxxj, 301-316.
22. TIEMANN, W.: Die individuelle intravenöse Behandlung Herzkranker mit Strophanthinpräparaten, Klin. Wchnschr., 1935, xiv, 913-917.
23. VAQUEZ, H., and LECONTE: Les injections intraveineuses de strophanthine dans le traitement de l'insuffisance cardiaque, Bull. et mem. Soc. med. d'hôp. d. Paris, 1909, xvii, 662-679.
24. WALLACE, E. W., and VAN DYKE, H. B.: Cumulative poisoning by squill derivatives and by ouabain, Jr. Pharmacol. and Exper. Therap., 1933, xlviii, 430-444.
25. WEESE, H.: Digitalis, 1936, G. Thieme, Leipzig.
26. WEESE, H.: Digitalisverbrauch und Digitaliswirkung Warmblüter, Arch. f. exper. Path. u. Pharmacol., 1929, cixl, 329-350.
27. WEESE, H.: Digitalisverbrauch und Digitaliswirkung; die Effektivdosen verschiedener Digitalisglykoside für das Herz, Arch. f. exper. Path. u. Pharmacol., 1928, cxxxv, 228-244.
28. ZAK, E.: Ueber Strophanthintherapie, Wien. klin. Wchnschr., 1936, xlix, 660-661.
29. ZWILLINGER, L.: Magnesium sulfuricum bei einer Strophanthinvergiftung, Wien. klin. Wchnschr., 1936, xlix, 594-595.
30. ZWILLINGER, L.: Über die Magnesiumwirkung auf das Herz, Klin. Wchnschr., 1935, xiv, 1429-1433.

THE CHOICE OF OVARIAN OR PITUITARY THERAPY FOR MENSTRUAL DISTURBANCES *

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DISTURBANCES in menstrual rhythm or in fertility are far more frequently due to hypofunction than to an increased rate of ovarian hormone production. Regularly recurring cycles of increasing and decreasing intensity of secretion are characteristic of the hormones of the ovary. In this cyclic character of its hormone production the ovary is unique among the glands, unless it be the anterior pituitary in its gonadotropic secretion. The adjustment of the ovarian cycle is influenced by so many and diverse factors that disturbances in its rhythm are not surprising. Such impinging factors include the activity of other organs, nutrient and endocrine materials, and possibly nervous system controls, as well as the indirect effects of deviations in health of other parts of the body. In its ovarian aspects, menstrual rhythm may be disturbed by alterations either in the duration or the intensity of follicular or luteal secretory activity. The duration as well as the intensity of the action of these hormones on uterus, breast, vagina and the brain will determine the character of the responses.

Failure of the ovarian cycle to be completed seems to be due to the failure of ovulation. This is far more common than was supposed a decade ago.¹ The occurrence of incomplete cycles may not preclude regularity in menstruation or occasional fertility in a given woman. Repeated failure of ovulation, however, is an obvious cause for sterility. So far as is known a corpus luteum is never formed in the human ovary unless ovulation has preceded.

There are thus three types of ovarian hormone disturbance: altered intensity of secretion of either of the hormones, altered duration of secretion, or incomplete cycles in which only the estrogenic hormone is produced.

If there were an increased intensity of estrogenic hormone production, the evidence should be found in the character of the endometrium, the vaginal epithelium, the mammary duct system, or the concentrations of hormone in blood or urine. The endometrial changes suggesting hyperestrinism are hyperplasia of the glands and excessive flowing.² But these results are also produced by long continued and essentially uninterrupted effect of estrogenic hormone, even in small amounts.³ Therefore endometrial hyperplasia cannot be accepted as evidence of hyperestrinism. From the study of vaginal smears, numerous cases of reduced stimulation are found, but excessive estrogenic effects have been seen only as a result of therapeutically administered estrogens. This method of diagnosis⁴ would be one of the

* Read at the New Orleans meeting of the American College of Physicians March 27, 1939.

best to demonstrate an altered intensity of hormone production, but to date no such cases have been reported. The mammary duct system has not yet been studied in human cases in sufficient numbers to allow its use as evidence on the point in question. Assays of blood and urine have been the chief sources of data for the diagnosis of quantitative variations in estrin secretion.⁵ But these diagnoses are open to serious criticism on two grounds: First, the assays do not distinguish between the three or more estrogens and their ester forms; second and more important is the fact that no assay method has yet been applied to a sufficient number of normally cycling and fertile women to define with certainty the normal standard of blood or urine content of these hormones. There can be no logical diagnosis of hyper- or hypofunction until the normal is defined. The problem is essentially the same as in interpreting basal metabolism, blood sugar concentration, or serum calcium level. Furthermore, difficulties are encountered because so much estrogenic hormone is destroyed by the liver⁶ that less than 10 per cent of injected estrin is recovered in the urine.⁷ Also, the excreted forms have a different biological activity than the original form secreted by the ovary,⁸ and quantitative recovery of estrogenic material from blood is difficult at best.

These details are cited in order to demonstrate the danger of accepting diagnoses of altered intensity of function based on any of the current methods. The vaginal epithelial studies of Papanicolaou and Shorr⁴ afford the nearest approach to quantitative assay, since the organism that produces the hormone also does the titrating, and only the end point has to be read. Even here the nutritional status of the woman may interfere, as in vitamin A deficiency. With the methods in use we can make diagnoses of hypofunction, based on tissue study (endometrium,⁹ breast, vaginal epithelium), and of distorted rhythm. Aside from the gynecological problems presented by occasional neoplasms, these syndromes can be described in terms of undersecretion or of shortened or prolonged secretion. No definite hypersecretion has been demonstrated. In connection with the secretion of the corpus luteum, chemical methods for estimating pregnandiol glycuronidate¹⁰ have provided a quantitative measure of luteal function. There is little evidence of cases of excessive luteal activity, or of unusually prolonged secretion of progesterone excepting in pregnancy.¹¹

The case is quite different in anterior pituitary secretion of the gonadotropic factor. Animal work demonstrates a variable gonadotropic potency of the pituitary gland at different stages in the life cycle.¹² In the senile or the castrate animal there is increased content of the hormone. This has been substantiated in a few human glands, but most of the information about the human comes from urinary assays.¹³ These cannot be held to measure the productivity of the intact human gland in any exact way. All the evidence points to one conclusion: the production and excretion of gonadotropic material by the pituitary is increased markedly whenever the ovaries are inactivated, removed, or atrophy spontaneously. Study of the urine by

methods recently described¹³ will justify differentiation of hyperfunction of the pituitary from other causes of disturbance in menstrual cycles. The methods will not yet allow of such certainty in discriminations between normal and reduced pituitary activity. Currently when there is subnormal ovarian action, without other recognized cause, hypopituitarism is being assumed. This undoubtedly includes many cases where other factors interfere with completely normal cycles of follicle and corpus luteum secretion. But clinical reasoning, based on analogies, accessory data, and results of therapy, makes it certain that some cases of ovarian hypofunction are secondary to pituitary hypofunction.¹⁴ Similarly, disturbed ovarian rhythm is in some cases due to disturbed timing or rate of secretion of the gonadotropic factors without which there is no ovarian activity. Consequently we may classify cases of ovarian hypofunction or atypical rhythm with regard to pituitary gonadotropic activity: as characterized by normal, increased or decreased function. At present the methods for substantiating the pituitary part of the diagnosis are elaborate enough to be limited to investigative clinics.

It is to be hoped that ultimately it will be possible to differentiate those cases with ovarian hypofunction secondary to primary pituitary failure from the cases with decreased ovarian function followed by increased pituitary activity. The latter cases will be expected *a priori* to be poorly adapted to therapy with pituitary gonadotropic materials. They seem to represent what can most simply be described as premature climacteric. This is based on the assumption that the climacteric is due to the failure of the ovaries from some cause other than pituitary failure.¹⁵ The assumption appears increasingly justified, although the possibility of nutritional deficits as causes for disturbance of the mechanism are not taken into account.

With such a state of partial diagnostic certainty the clinician is called upon to treat a variety of disorders of menstrual regularity and of sterility. Omitting those in whom there is reason to believe that anatomic anomalies, neoplasms, infectious processes, poor hygiene, or male responsibility (sterility) are the chief concerns, we return to the dictum: the symptoms and findings, if endocrine, are probably due to deficient amount of secretion or to prolongation of the follicular secretion phase. This generalization holds true from menarche to menopause, although for varying reasons. There is no way by which to explain the occurrence of menorrhagia in one case, oligomenorrhoea in another, amenorrhoea in a third, variations in cycle length in a fourth, variations in amount of flow at different times in a fifth woman. In fact it is most common to find all these features occurring at one time or another in the same patient, demonstrating that these are relatively incidental features of the underlying cause: ovarian underactivity.¹⁴

The first inclination of the clinician some years ago was to use substitution therapy with estrogenic substances, to augment the supply which was then thought and is now known to be inadequate for normal menstrual cycles. This therapy will often relieve the subjective complaints of the

autonomic and mental type which are characteristic of the climacteric. Similar symptoms occurring early in the reproductive period¹⁶ do not prove the imminence of the climacteric, for they may continue through many years. Their relief, while gratefully received by the patient, must not be taken as evidence of cure. We know that ovarian secretions do not stimulate the ovaries. Hypofunction is therefore not helped by ovarian hormone substitution therapy. There may be temporary improvement in menstrual rhythm, sometimes reduction in menorrhagia, but there is seldom evidence of improved fertility from such treatment. This is obviously the most important test of its adequacy.

A disadvantage of ovarian substitution therapy is the inhibiting effect of the estrogenic hormone¹⁷ on the pituitary production of the gonadotropic hormone. Estrin is therefore held to be contraindicated if continued pituitary function and ovarian rhythm with fertility are the clinical goals. At least in animals it is possible by the use of large doses of estrin to interrupt cyclic action, disturb fertility, and therefore to simulate some of the clinical syndromes described. There is a little evidence that with the use of large doses of estrin given at appropriate times, and for brief periods, the pituitary secretions may be made to induce ovulation.¹⁸ Unfortunately the problem of inhibition of the pituitary by the estrogenic hormone, and the question of initiating ovulation by stimulating the pituitary with estrogen, both require quantitative study of a type which has heretofore been all but impossible. Methods are becoming available to make such theories susceptible of test.

Until more definite information is available concerning the effects of clinical doses of estrogens on the pituitary, and therefore indirectly on the ovaries, it is the part of wisdom to limit the use of estrogenic hormone preparations to those cases which can be classed as menopausal. If patient and physician agree that there is no need to strive for regular cycles, to maintain or restore fertility, or to be concerned about anything save subjective relief from distress, then the simplest course is to use sufficient doses of estrin to accomplish this relief.¹⁹ The route of administration may be by injection of aqueous or oil solutions, by vaginal suppositories, or by oral administration. The aqueous extracts are of low potency, and seldom used. Oil solutions are available in a variety of potencies. Until the ultimate fate of these oils as foreign bodies is settled favorably they must remain under suspicion as poor therapeutic vehicles for intramuscular injection. The introduction of large doses in oil at long intervals gives a type of control which is inferior to that given by smaller doses spaced at shorter intervals. The latter is possible by oral treatment. Vaginal suppositories are useful chiefly when local effects on the vaginal mucosa are sought. The use of tablets or capsules of estrogens by mouth is an effective way to introduce adequate amounts of these hormones. The cost of the necessarily larger oral doses is no greater than that of the injection of therapeutically equivalent amounts when the cost of the injections is added to that of the hormone. With the greater convenience and more uniform control of symptoms, ad-

ministration by mouth is the recommended method. Doses vary widely. Minimum effective amounts for maintenance seem to be about 0.1 mg. (100 gamma, or 1000 units) of estrone. The maximum doses required to secure prompt relief from the more severe disturbances may run to 1.5 mg. (1500 gamma, or 15,000 units) in divided doses daily. Such large doses can be reduced gradually after the first few days or weeks.

The recommended plan of therapy is to use sufficient material to give relief, reducing the amount gradually but always keeping it high enough for real subjective satisfaction. Such a course may have to be continued for many years. At times it may be interrupted if symptoms are in abeyance, but it need not be interrupted for any reason save economy. The occurrence of flowing should not be the occasion for any alteration in dosage unless by trial there is greater comfort with more or less estrin at such times. It may be said, in summary, that menopause symptoms may be treated as due to the menopause even though flows persist.

When, however, there is the desire to restore menstrual rhythm or to improve fertility, the therapy should be based on an attempt to stimulate the ovaries.¹⁴ For this purpose the chorionic hormone (A. P. L.), derived from the urine of pregnant women, is not satisfactory. It does not stimulate the human ovaries, and its use does not initiate ovulation in women. Stimulation of ovarian functions may be attempted with some hope of success by use of two types of gonadotropic preparations: that from genuine pituitary, or that from the serum of pregnant mares. Preparations of these two types may be administered with safety hypodermically, in spite of the protein content of most of them. Local reactions to the injection of pituitary materials are unpleasant but usually not dangerous. Little benefit is to be expected from the use of a few doses. The active gonadotropic substances are water soluble, they act quickly and only for a few hours. Therefore the use of a series of doses given daily or on alternate days is the minimum that is promising. Such series will usually have to be repeated with a number of successive cycles before results are achieved. Since the ovaries are typically cyclic in all their activities, it is not surprising that cycles of stimulatory therapy are necessary. Cystic follicles may be produced²⁰ if continuous gonadotropic injection is practiced. Since follicular growth becomes more marked at the onset of a menstrual flow, it has seemed appropriate to commence the successive series of doses at the beginning of each flow. Such a period of treatments, amounting to 5 to 15 doses, is discontinued not later than the fifteenth day, the approximate time of a normal ovulation.

Though the hypodermic injection of even very large doses of gonadotropic extracts has not led to ovulation and the formation of corpora lutea, there is some evidence that intravenous injections will lead to ovulation.²¹ The use of pituitary extracts intravenously is still accompanied by some hazard because of their high protein content, but the employment of an extract from the serum of pregnant mares in highly concentrated form has the advantage here of being almost free from protein. If it is to be used intravenously it is probably wise to precede such injection by hypodermic doses to

stimulate the follicle to maturity. Also it is known that once a follicle has been made to ovulate, and the corpus luteum has been formed, pituitary stimulation is still required to sustain the action of the corpus luteum.²² Therefore it may be necessary to employ a few more daily doses of the hypodermic type to secure optimal luteal activity.

Reflection on these suggestions calls attention at once to the large number of doses required, and the need for a sustained effort for several months if results are to be maintained once they are secured. Even more one is led to wonder how the size of dose and the necessary number of doses may be estimated. At this point the vaginal smear technic is of help, for it enables the clinician to determine the extent of follicular secretion during the first two weeks of the cycle. The procedure is painless, takes little time, and is not expensive if done by someone who is handling a significant number of such patients. It is not adapted to general practice or occasional use. To determine the adequacy of luteal secretion, and to detect ovulation followed by corpus luteum formation, there are two possible methods: endometrial biopsy⁹ or pregnandiol estimation¹⁰ in 24 hour urine samples. Biopsies have disadvantages, especially in the danger of interrupting a possible pregnancy. Also, save in very experienced hands, the study of the tissue does not yield quantitative results. The estimation of pregnandiol excretion is better here, for the standards based on an available series of normals give some measure of the amount of this compound which should appear normally in the third and fourth weeks of the cycle.¹¹ The disadvantages include the collection of a series of 24 hour urine samples for a week or more, and a laborious and very costly chemical method. Perhaps the best that can be said of this urinary method and of the frequent use of biopsies is that their study has made possible an improved accuracy in diagnosis of anovulatory flowing, deficient action of progesterone, and improvement in these functions under therapy as outlined above.

Therefore the practitioner who is confronted with the need for treating hypofunction of the ovaries and who desires to attempt stimulation with gonadotropic extracts had best employ cycles of 5 to 15 daily doses, hypodermically, repeating the courses with the onset of each flow. If amenorrheic periods occur, the cycles of treatment may be carried out every four weeks until some flow occurs to mark a cycle of activity. For most hopeful results it remains necessary to subject such cases to semi-quantitative studies before and during therapy, by methods which are still available only in the well equipped endocrine-gynecological clinics.

BIBLIOGRAPHY

1. NOVAK, E.: Endocrine mechanisms in certain functional gynecologic disorders, *Surg., Gynec. and Obst.*, 1935, ix, 330.
BARTELMEZ, G. W.: Menstruation, *Physiol. Rev.*, 1937, xvii, 28.
ROCK, J., BARTLETT, M. K., and MATSON, D. D.: The incidence of anovulatory menstruation among patients of low fertility, *Am. Jr. Obst. and Gynec.*, 1939, xxxvii, 3.
2. FRANK, R. T., SPIELMAN, F., and GOLDBERGER, M. A.: Present endocrine diagnosis and therapy, *Jr. Am. Med. Assoc.*, 1934, ciii, 393.

3. BURCH, J. C., McCLELLAN, G. S., JOHNSON, C. D., and ELLISON, E. T.: The diagnosis and classification of menstrual disorders, *Jr. Am. Med. Assoc.*, 1937, cviii, 96.
4. PAPANICOLAOU, G. N., and SHORR, E.: Action of ovarian follicular hormone in the menopause, as indicated by vaginal smears, *Am. Jr. Obst. and Gynec.*, 1936, xxxi, 806.
5. ALBRIGHT, F., and HALSTEAD, J. A.: Studies on ovarian dysfunction, *New England Jr. Med.*, 1935, ccxii, 250.
6. ISRAEL, S. L., MERANZE, D. R., and JOHNSTON, C. G.: Inactivation of estrogen by the liver: fate of estrogen in heart-lung and heart-lung-liver perfusion systems, *Am. Jr. Med. Sci.*, 1937, cxciv, 835.
 GOLDEN, J. B., and SEVRINGHAUS, E. L.: Inactivation of estrogenic hormone of the ovary by the liver, *Proc. Soc. Exper. Biol. and Med.*, 1938, xxxix, 361.
7. KEMP, T., and PEDERSEN-BJERGAARD, K.: Absorption and excretion of estrone by the human organism, *Lancet*, 1937, ii, 842.
 MAZER, C., and ISRAEL, S. L.: Optimal dosage of estrogens: experimental and clinical evaluation, *Jr. Am. Med. Assoc.*, 1937, cviii, 163.
8. SCHOELLER, W., DOHRN, M., and HOHLWEG, W.: Problem of standardization of follicle hormone and its derivatives, *Klin. Wchnschr.*, 1935, xiv, 339.
9. CAMPBELL, R. E., LENDRUM, F. C., and SEVRINGHAUS, E. L.: Endometrial histology and pathology as revealed by biopsy method, *Surg., Gynec. and Obst.*, 1936, lxiii, 724.
10. VENNING, E. H.: Further studies on the estimation of small amounts of sodium pregnandiol glycuronidate in urine, *Jr. Biol. Chem.*, 1938, cxxvi, 595.
11. WILSON, R. B., RANDALL, L. M., and OSTERBERG, R. E.: Studies on pregnandiol, *Am. Jr. Obst. and Gynec.*, 1939, xxxvii, 59.
12. LAUSON, H. D., GOLDEN, J. B., and SEVRINGHAUS, E. L.: The gonadotropic content of the hypophysis throughout the life cycle of the normal female rat, *Am. Jr. Physiol.*, 1939, cxxv, 396.
13. HELLER, C. G., and HELLER, E. J.: Gonadotropic hormone: urine assays of normally cycling, menopausal, castrated, and estrin treated human females, *Jr. Clin. Invest.*, 1939, xviii, 171.
14. CAMPBELL, R. E., and SEVRINGHAUS, E. L.: Pituitary gonadotropic extracts for treatment of amenorrhea, menorrhagia, and sterility, *Am. Jr. Obst. and Gynec.*, 1939, xxxvii, 913.
15. WATSON, B. P., SMITH, P. E., and KURZROK, R.: Relation of the pituitary gland to the menopause, *Am. Jr. Obst. and Gynec.*, 1938, xxxvi, 562.
16. SCHNEIDER, P. F.: A syndrome suggestive of ovarian deficiency, *Am. Jr. Obst. and Gynec.*, 1936, xxxi, 782.
17. ALLEN, E., and DIDDLE, A. W.: Ovarian follicular hormone effects on ovaries, *Am. Jr. Obst. and Gynec.*, 1935, xxix, 83.
 FOSS, G. L.: Temporary postponement of menstruation by estradiol benzoate, *Brit. Med. Jr.*, 1937, vii, 10.
18. FEVOLD, H. L., HISAW, F. L., and GREEP, R.: Effect of oestrin on the activity of the anterior lobe of the pituitary, *Am. Jr. Physiol.*, 1936, cxiv, 508.
19. SEVRINGHAUS, E. L.: Relief of menopause symptoms by estrogenic preparations, *Jr. Am. Med. Assoc.*, 1935, civ, 624.
20. HISAW, F. L.: Personal communication.
 FEVOLD, H. L.: The follicle stimulating and luteinizing hormones of the anterior pituitary, Chap. xvii in "Sex and internal secretions," by ALLEN, E., et al., 1939, Williams and Wilkins Co., Baltimore.
21. FOSTER, M. A., and HISAW, F. L.: Experimental ovulation and resulting pseudopregnancy in anestrus cats, *Anat. Rec.*, 1935, lxii, 75.
 DAVIS, M. E., and KOFF, A. K.: Experimental production of ovulation in human subjects, *Am. Jr. Obst. and Gynec.*, 1938, xxxvi, 183.
22. HISAW, F. L.: The physiology of menstruation in *Macacus rhesus* monkeys, *Am. Jr. Obst. and Gynec.*, 1935, xxix, 638.

A NEW MATHEMATICAL METHOD FOR THE EVALUATION OF ENDOGENOUS INSULIN SECRETION*

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It has been said that insulin administration cannot be calculated by mathematical equations; that no one knows the exact amount of carbohydrate that will be metabolized by a given amount of insulin.¹

Probably every physician of experience in the treatment of diabetes mellitus has been puzzled at times to know how much insulin a given patient requires. We have all been confronted with the widely varied responses of different patients, as well as of the same patient at different times, to comparable doses of insulin.

This dissimilarity of response of different patients to comparable doses, or of the same patient at different times to the same dose of insulin, has defied satisfactory explanation largely because the factor of endogenous insulin secretion has been unpredictable. Because it has not been possible heretofore to estimate the physiological activity of the pancreas and other organs concerned with carbohydrate metabolism in terms of units of insulin, the administration of insulin has been largely an empirical procedure of trial and error, with the ever present danger of producing a hypoglycemia with too large a dose, or failing to accomplish the desired reduction of blood sugar with too small a dose.

We are all familiar with the repeated observation that patients in acidosis and coma "soak up insulin like a sponge," and heroic doses of insulin are required; yet we are often deterred from giving a single large dose by the fear of overdosage, and the desired result is unduly delayed by frequent repetition of small doses over a considerable period of time.

Given a patient with a fasting blood sugar of, say 300 mg. per 100 c.c.—how much insulin is it safe to give, and how small a dose will accomplish the desired result—namely, a rapid lowering of the blood sugar to normal limits?

Alexis F. Hartmann,² in 1925, described a mathematical calculation, by which, given a patient's body weight and blood sugar, the dosage of insulin can be calculated with sufficient accuracy so that, *theoretically*, the blood sugar can be reduced from any level to any point desired with a single dose of insulin. While the method has certain limitations which will be emphasized later, Hartmann's contribution has not received the notice and wide application it deserves.

It was while working with this method that we discovered a formula for measuring the approximate amount of insulin secreted in the body. This factor of endogenous insulin secretion is extremely important in any consideration of exact insulin dosage, yet, so far as we have been able to

* Received for publication July 19, 1938.

learn, nobody has heretofore devised any method of calculating the insulin secretion in a given patient. The purpose of this paper is to present a method of calculating insulin dosage, based on Hartmann's work, but which for the first time, takes into account the heretofore unpredictable factor of endogenous insulin. This method in our hands has, to a large extent, eliminated the empiricism and guesswork from insulin therapy.

We do not mean to imply that pathological physiology can be reduced to mathematical formulae. What we hope to accomplish is to elucidate a new method of measuring a physiological function which has no other yardstick. With due appreciation of its limitations and inaccuracies, we believe this method may be of vital importance in arriving at a better understanding of the physiology of diabetes mellitus. We present the method as a clinical experiment and hope that it will receive further trial by others.

Since a thorough understanding of Hartmann's calculation of insulin dosage is necessary to an understanding of its later application to the measurement of endogenous insulin secretion, the method will be described in some detail.

METHOD OF COMPUTING INSULIN DOSAGE, GIVEN THE BLOOD SUGAR AND THE BODY WEIGHT (See table 1)

According to Hartmann,² the weight of the body fluids and the soft tissues is taken to be $\frac{2}{3}$ times the body weight. Thus, if the body weight is 60 kg., the soft tissue is $\frac{2}{3}$ times 60 kg. = 40 kg. or 40,000 gm. (Allowance should be made for excess fat in obese patients.)

The concentration of glucose throughout the body, exclusive of the skeletal structures, is assumed to be the same as that of the blood. Thus, if the blood sugar is 0.35 per cent or 350 mg. per 100 c.c., then the total amount of glucose in the body is 0.35 per cent of the weight of the soft tissue, or $0.0035 \times 40,000 \text{ gm.} = 140 \text{ gm.}$

Similarly, if the blood sugar were 0.10 per cent or 100 mg. per 100 c.c., the total amount of glucose in the body would be $0.001 \times 40,000 \text{ gm.} = 40 \text{ gm.}$

Whence it is clear that to reduce the blood sugar from 0.35 per cent (350 mg. per 100 c.c.) to 0.10 per cent (100 mg. per 100 c.c.) it would be necessary not only to oxidize the excess sugar in the blood, but the total excess sugar in all the soft tissues, which in the above case would be 140 gm. — 40 gm. = 100 gm.

Putting it another way, to reduce the concentration of glucose from 0.35 per cent to 0.10 per cent the glucose to be oxidized = (0.35 per cent — 0.10 per cent) times the weight of the soft tissue or 0.25 per cent of 40,000 gm., whence $0.0025 \times 40,000 \text{ gm.} = 100 \text{ gm.}$

Since one unit of insulin will permit the oxidation of approximately two gm. of glucose, the amount of insulin required equals 100 divided by

two equals 50 units. Also, if the patient is given glucose intravenously, one additional unit is given for each two gm. of glucose injected.

The foregoing is, in principle and application, Hartmann's method of computing insulin dosage. However, such a calculation does not take into account the variable factor of how much endogenous insulin may be secreted at the same time insulin is administered parenterally.

We feel that allowance must be made for possible pancreatic insulin secretion if one is to avoid the possibility of dangerous hypoglycemic reactions, and that it would not be safe to give the entire calculated dose of 50 units at one time, and that therefore, pending evaluation of endogenous insulin, a smaller dose should be tried, say 20 to 30 units, plus an amount sufficient to cover the glucose injected.

It is true that patients in acidosis and coma secrete very little insulin. Nevertheless, all patients in coma are not necessarily total diabetics, and even though the foregoing calculation of insulin is based on 1 unit per

TABLE I.*

Body weight	60 kg. = 60,000 gm.	
Soft tissue $2/3 \times 60$ kg.	= 40 kg. = 40,000 gm.	
Blood sugar	0.35%	
Desired blood sugar	0.10%	
<hr/>		
Desired fall in blood sugar	0.25%	
Total glucose to be oxidized	= 0.25% of soft tissue	
	= $0.0025 \times 40,000$ gm.	= 100 gm.
Insulin required	= $100 \div 2$	= 50 U
Infusion 10% glucose 600 c.c.	= 60 gm. glucose	
Insulin to cover glucose given	= $60 \div 2$	= 30 U
Total insulin (single dose)		80 U

* Hartmann's calculation of insulin dosage.

2 gm. of glucose instead of 1.5 gm., there is grave possibility of overdosage if the pancreas happens to secrete more insulin than would be expected in a total diabetic. This is especially true in children in whom the margin of safety is much smaller than it is in adults, and in whom relatively small doses may cause hypoglycemia.

For example, in the case of L. M., aged six years (case 1), the blood sugar was 0.37 per cent before the noon meal, which contained 38 gm. of available glucose. The calculated insulin dosage necessary to reduce the blood sugar to 0.12 per cent, plus an amount sufficient to cover the available glucose in the noon meal, was 35 units. Not knowing as yet what to expect from the pancreas, we gave her only 20 units. Four hours later her blood sugar was 0.03 per cent or 30 mg. per 100 c.c. According to our subsequent calculation she had secreted over 20 units of insulin, which, together with the 20 units injected caused a dangerous degree of hypoglycemia.

DEFINITION OF THE TERM "ENDOGENOUS INSULIN"

Of course, in attempting to predict on a mathematical basis what the blood sugar will be after a given dose of insulin, one must realize that

there are many complicating factors which are potential sources of error. The constant ebb and flow of glycogen, the influence of other glands of internal secretion such as the pituitary, the effect of epinephrine on glycogenolysis, exercise, diets not all eaten or well tolerated, varying absorption of carbohydrate—all these are variables which influence the result. However, the net effect of the interplay of all these variable factors concerned with carbohydrate metabolism is to raise or lower the concentration of glucose a definite percentage.

The result, in blood sugar percentage, may be readily calculated as grams of glucose oxidized and (or) stored as glycogen, or added to the blood and soft tissues. It does not make any difference, so far as the concentration of glucose in the blood and other soft tissues is concerned, whether a given amount of glucose be partly or wholly oxidized or partly or wholly stored in the glycogen reservoirs, or partly oxidized and partly stored as glycogen. The number of grams of glucose above or below the original concentration is equivalent to the calculated effect of a corresponding amount of insulin, and may be expressed mathematically in terms of units of insulin on the basis of one unit of insulin per 2 gm. of glucose.

Our calculations indicate that the net effect of the functional activity of the liver, pancreas and other glands of internal secretion can be predicted with considerable accuracy, and that the resulting concentration of glucose in the soft tissues is the same as the concentration which might be expected to result from the utilization of a definite amount of insulin.

We therefore employ the term "endogenous insulin" as a quantitative expression of the sum total of the functional activity of all the factors concerned in carbohydrate metabolism as if the pancreas were the only factor involved.

Estimation of Endogenous Insulin. The fasting blood sugar is brought rapidly within the desired range (below 180 mg. per 100 c.c.) according to Hartmann's method (taking care to give somewhat less than the maximum calculated doses of insulin pending evaluation of endogenous insulin), after which the patient is started on a computed, weighed diet. The blood sugar is determined four hours after each meal and the maintenance insulin dosage and endogenous secretion are estimated as follows:

Example (See table 2)

Given a child weighing 18.75 kg., with a blood sugar of 225 mg. per 100 c.c., on a diet which contains 42 gm. available glucose in each meal (table 2).

In this problem the weight of the body fluids and soft tissues is $\frac{2}{3}$ (18,750 gm.) or 12,500 gm.

Assuming endogenous secretion to be zero, the effect of ingesting 42 gm. or 42,000 mg. of glucose would be to raise the blood sugar a definite amount. This is obtained by dividing the number of mg. of ingested glucose by the

number of hundred grams of soft tissue. Since the soft tissue weighs 12,500 gm. (or 125 hundred gm.) the calculated rise in blood sugar is 42,000 divided by 125 = 0.336 per cent. Adding this to the initial blood sugar of 0.225 per cent the calculated peak of the blood sugar curve is 0.561 per cent (still disregarding the presence of both exogenous and endogenous insulin).

Suppose we now desire to reduce the blood sugar from the estimated peak of 0.561 per cent to 0.121 per cent, a fall of 0.440 per cent. Then the total glucose to be oxidized would be $0.0044 \times 12,500 \text{ gm.} = 55 \text{ gm.}$ (The same figure would be obtained by computing the weight of glucose oxidized by reducing the blood sugar from the initial level of 0.225 per cent to 0.121 per cent and adding the number of grams of glucose ingested.)

The number of grams of glucose (55) divided by two gives the estimated insulin required.

TABLE II

Body weight, 18.75 kg.	18,750 gm.
Weight of soft tissue	12,500 gm.
Ingested glucose, 42 gm.	42,000 mg.
Initial blood sugar (b.s.)	0.225%
Expected rise in b. s. (42,000/125)	0.336%
Estimated peak b. s.	0.561%
Desired b. s.	0.121%
Desired fall in b. s.	0.440%
Total glucose to be oxidized (0.0044) (12,500)	55 gm.
Estimated insulin required 55/2	27½ U
Endogenous insulin	17½ U (?)
Insulin injected	10 U
Actual result b. s.	0.170%
Actual fall in b. s. (0.561-0.170)	0.391%
Actual total glucose oxidized (0.00391) (12,500)	49 gm.
Actual total insulin used (49/2)	24½ U
Actual amount of endogenous insulin (24½-10)	14½ U

Now, not having any previous calculations, we do not have any measure, as yet, of the functional activity of the pancreas. Therefore instead of injecting 27 units we inject only 10. The resultant blood sugar is 0.170 per cent, a drop of 0.391 per cent from the estimated peak, from which we calculate that the total amount of glucose actually oxidized, including soft tissue glucose plus ingested glucose, is $0.00391 \times 12,500 = 49 \text{ gm.}$

Dividing by two, the total insulin actually used (10 units injected plus endogenous insulin) was 24½ units, whence it is perfectly clear that the body must have provided approximately 14½ units of insulin.

This calculation is repeated for each meal on successive days until we have a very good idea how many units of endogenous insulin are available at certain times under the stimulus of a given amount of carbohydrate ingested. Provided one makes sure that all of the diet is taken, the output of endogenous insulin (after recovery from coma and ketosis) does not vary as much as one might expect. In fact the variation from day to day is

within sufficiently narrow limits that we soon strike an average estimate of the amount of endogenous insulin produced at different times during the day (table 6). By subtracting this amount from the total requirement we arrive at a very exact measure of the maintenance dosage of exogenous insulin required.

It has been surprising and exceedingly gratifying to us to find that we have repeatedly been able to predict and to obtain a blood sugar almost exactly what we had estimated it should be after a given intake of carbohydrate and an exactly calculated dose of insulin.

Case 1. L. M., aged five years 10 months, was first seen by M. M. on September 18, 1934, at which time she presented the picture of acidosis with air hunger, beginning coma, dehydration and malnutrition. Her urine contained acetone, diacetic acid and sugar four plus. She had been vaccinated against smallpox two weeks before and had developed vaccinia one week thereafter. The general health had always been good. There had not been any previous history or knowledge of diabetic symptoms. One maternal aunt had diabetes; otherwise the family and past histories were negative. She was admitted to the Childrens Hospital at 3:00 p.m., at which time the blood sugar was 0.37 per cent. She was given 15 units insulin subcutaneously plus 200 c.c. 10 per cent glucose (20 gm. glucose) and 10 units insulin intravenously. At 8:00 p.m., the blood sugar was 0.29 per cent. She was then given 20 gm. of glucose plus 20 units of insulin in 500 c.c. of Hartmann's solution subcutaneously. At 7:45 the next morning the blood sugar was 0.10 per cent. She was then started on a diet of P 50-F 100-C 75, containing 38 gm. available glucose in each meal. Two days later the diet was changed to P 50-F 75-C 90, containing 42 gm. available glucose. Blood sugars were taken before each meal and the insulin requirement and endogenous insulin secretion calculated. The results are tabulated in table 3.

TABLE III
(Breakfast)

Case 1 (L.M.)	9/19	9/20	9/21	9/22	9/23	9/24
Weight of soft tissue in gm.	12,800	12,800	12,400	12,400	12,400	12,400
Ingested glucose	38 gm.	38 gm.	42 gm.	42 gm.	42 gm.	42 gm.
Initial b. s.	0.100	0.420	0.480	0.400	0.340	0.215
Expected rise	0.297	0.297	0.338	0.338	0.338	0.338
Estimated peak	0.397	0.717	0.818	0.738	0.678	0.553
Desired b. s.	0.100	0.120	0.180	0.100	0.120	0.153
Desired fall	0.297	0.597	0.638	0.638	0.558	0.400
Estimated total glucose to be oxidized	38 gm.	76 gm.	79 gm.	79 gm.	69 gm.	50 gm.
Estimated amount of insulin required	19 U	38 U	39½ U	39½ U	34½ U	25 U
Estimated secretion of endogenous insulin	?	?	19½ U?	19½ U?	19½ U?	20 U?
Insulin injected	0	10 U	20 U	20 U	10 U	10 U
Actual result	0.370	0.210	0.225	0.095	0.140	0.100
Actual fall	0.027	0.507	0.593	0.643	0.538	0.453
Actual total glucose oxidized*	3½ gm.	65 gm.	73½ gm.	79.7 gm.	67 gm.	56 gm.
Actual total insulin *	1¾ U	32½ U	36¾ U	39¾ U	33½ U	28 U
Insulin injected	0	10 U	20 U	20 U	10 U	10 U
Actual secretion of endogenous insulin *	1¾ U	22½ U	16¾ U	19¾ U	23½ U	18 U

* Approximate.

TABLE III (continued)
(Dinner)

Case 1 (L.M.)	9/19	9/20	9/21	9/22	9/23	9/24
Weight of soft tissue in gm.	12,800	12,800	12,400	12,400	12,400	12,400
Ingested glucose	38 gm.	38 gm.	42 gm.	42 gm.	42 gm.	42 gm.
Initial b. s.	0.370	0.210	0.225	0.095	0.140	0.100
Expected rise	0.297	0.297	0.338	0.338	0.338	0.338
Estimated peak	0.667	0.507	0.563	0.433	0.478	0.438
Desired b. s.	0.120	0.110	0.125	0.100	0.140	0.100
Desired fall	0.547	0.397	0.438	0.333	0.338	0.338
Estimated total glucose to be oxidized	70 gm.	51 gm.—	54 gm.+	41 gm.	42 gm.	42 gm.
Estimated amount of insulin required	35 U	25½ U	27 U	20½ U	21 U	21 U
Estimated secretion of endogenous insulin	?	20 U ?	17 U ?	17 U ?	16 U ?	17 U ?
Insulin injected	20 U	5 U	10 U	4 U	5 U	3 U
Actual result	0.030	0.170	0.170	0.080	0.130	0.130
Actual fall	0.637	0.337	0.393	0.353	0.348	0.308
Actual total glucose oxidized *	81½ gm.	43 gm.	48.7 gm.	44 gm.	43 gm.	38 gm.
Actual total insulin *	40¾ U	21½ U	24½ U	22 U	21½ U	19 U
Insulin injected	20 U	5 U	10 U	4 U	5 U	3 U
Actual secretion of endogenous insulin *	20¾ U	16½ U	14½ U	18 U	16½ U.	16 U

* Approximate.

The following points should be noted in table 3.

1. The morning after admission the morning blood sugar was 0.10 per cent. The patient had just recovered from coma. It was desired to see how much glucose she could oxidize without any exogenous insulin. She was therefore given her breakfast, containing 38 gm. available glucose, and insulin was withheld. On the basis of 1 unit of insulin per 2 gm. of glucose in her breakfast, her insulin requirement to keep her blood sugar at approximately 0.10 per cent was 19 units. The actual result was a blood sugar of 0.370 per cent, a fall of 0.027 per cent from the estimated peak; from which it was calculated she actually oxidized only approximately 3½ gm. of glucose. She therefore secreted approximately 1¾ ± units of insulin. From then on she made a very rapid recovery and her endogenous insulin output in the morning varied between 16 and 24 units.

2. The same noon (September 19), because she had secreted so little insulin in the morning, she was given 20 units. The result was a drop from 0.370 per cent to a hypoglycemia of 0.03 per cent, which, as previously brought out, showed she actually oxidized (or stored in her glycogen reservoirs) approximately 81½ gm. of glucose, which was equivalent to 40¾ units of insulin, or 20¾ units more than was injected. Whence came this extra insulin except from an endogenous source? During the next five days the endogenous insulin available for the noon meal varied from 14 to 18 units.

3. That a basis of 1 unit of insulin per 2 gm. of glucose in calculating the insulin requirement, and that this method of computing endogenous

insulin is sufficiently accurate to be practical, are well shown in columns 9/22 and 9/23, in which the desired blood sugars on two successive days after breakfast were 100 and 120, and after dinner 100 and 140, and the actual results obtained were 95, 140, 80 and 130 respectively.

4. The blood sugars before breakfast shown in table 3 were consistently high. This was because the morning blood sugar could not be controlled satisfactorily without a midnight dose of insulin. It is well known that it is difficult to keep severe diabetics sugar free in the morning on three doses of insulin per day. According to Hartmann: "If the diabetes is very severe and approaches the 'total diabetic' state, the effect of the evening injection will be gone long before the next morning and the blood sugar may mount well beyond the threshold. In that case the patient cannot be kept entirely sugar free on three injections and must be given a fourth at midnight." In this patient a dose of insulin before supper, sufficiently large to keep the morning blood sugar below the renal threshold caused mild hypoglycemic reactions at about midnight. We are of the opinion that to apply our method of estimating the exact insulin requirements throughout the 24 hours, one should not only give four doses of insulin per day but also a midnight feeding. We did not do this because of lack of laboratory assistance at night. (No calculations for supper are presented because of this lack of any midnight blood sugar determinations to check the results. The procedure would be the same at 6:00 p.m. and at midnight as for the breakfast and dinner calculations.)

After sufficient blood sugar determinations three times a day to give a satisfactory estimate of the average amount of insulin secretion to be expected, blood sugars were taken only once a day, before breakfast, and the patient put on 10, 5 and 10 units before breakfast, dinner and supper.

The patient's glucose tolerance increased rapidly and by the thirteenth to the eighteenth day after admission the morning blood sugar varied from 0.155 per cent to 0.240 per cent, with an average morning blood sugar of 0.184 per cent.

She was discharged October 5, 1936, and readmitted two days later with an acute upper respiratory infection, temperature 105.0° F. This time she was in the hospital six days, during which time her diabetes was under control, with a morning blood sugar which varied from 0.085 per cent to 0.190 per cent, with an average of 0.136 per cent.

This case has been presented in considerable detail in order to explain the application of the method of estimating endogenous insulin.

Case 2 was one of severe diabetic coma in a 10 year old girl. All pertinent data relative to her clinical course are summarized in tables 4 and 5.

LIVER FAILURE DURING COMA

Table 5 is tabulated in a different form to show how the physiologic depression of carbohydrate oxidation and glycogenesis during coma may be expressed in terms of insulin deficit.

TABLE IV

Case 2 (O.P.). Aged 10 years, 2 mos. Admitted December 3, 1937.

Condition: Coma, acidosis, dehydration

Date	Blood Sugar			Glucose (parenteral)	Insulin
12/3	Noon	0.560	500 c.c. 10% glucose in saline (50 gm.) 500 c.c. 10% glucose in Hartmann's sol. (50 gm.)		40 U 25 U 30 U 20 U 15 U
	4.00 p.m.	0.640			
	8.30 p.m.	0.400			
	12.00 m.	0.290			
	a.m.	Noon	p.m.	Diet	Insulin
12/4	0.040	0.260	0.220	C 150 P 47 F 40 C 180 P 60 F 60 Lunch and noon insulin omitted; 	

TABLE V
(Case 2)

Date	12/3				12/4					12/5
Hour	noon	4 p.m.	8 p.m.	12 m.	8 a.m.	1 p.m.	5 p.m.	8 p.m.	12 m.	4 a.m.
Gm. soft tissue	13,300									
Blood sugar	0.560	0.640	0.400	0.290	0.040	0.260	0.220	0.070*	0.125*	0.180*
Gm. G in diet					26	26		17.6	17.6	17.6
Gm. G parenteral	100				50					
Theoretical peak ^a	1.310	0.640	0.400	0.290	0.610	0.455	0.220	0.200	0.255	0.310
Insulin injected	65 U	30 U	20 U	15 U	25 U	20 U	10 U	5 U	5 U	5 U
Theoretical fall ^b	0.980	0.450	0.300	0.225	0.375	0.300	0.150	0.075	0.075	0.075
Theoretical result (x)	0.330	0.190	0.100	0.065	0.235	0.155	0.070	0.125	0.180	0.235
Actual result	0.640	0.400	0.290	0.040	0.260	0.220	?	?	?	0.040
Difference above x	0.310	0.210	0.190		0.025	0.065				
Difference below x				0.025						0.195
Gm. G above x ^c	41	28	25		3	8				
Gm. G below x ^d				3						26
Insulin deficit	20 U	14 U	12½ U		1½ U	4 U				
Insulin surplus				1½ U						13 U
Column number	1	2	3	4	5	6	7	8	9	10

^a Theoretical peak blood sugar if both endogenous and exogenous insulin were zero

$$= \text{initial blood sugar} + \frac{\text{mg. G administered}}{\text{no. of 100 gm. soft tissue}}.$$

^b If endogenous insulin were zero, theoretical fall = $\frac{\text{mg. G oxidized by insulin injected}}{\text{no. of 100 gm. soft tissue}}.$

^c and ^d Gm. glucose remaining in blood and soft tissue above or below the amount theoretically present after oxidation by a given dose of insulin if the endogenous insulin were zero.

* Estimated.

? Unknown.

During the toxic stage of coma and acidosis there is a suppression of liver function as well as of pancreatic function, and the failure of large doses of insulin to lower blood sugar in accordance with theoretical calculations during coma is due to failure of the glycogen storage mechanism. The exact rôle of insulin in relation to both oxidation of glucose and glycogenesis is speculative. At any rate, as long as the glycogen storage function of the liver is suppressed by the toxemia incident to coma, it requires much larger doses of insulin to remove a given quantity of sugar from the soft tissues than it does after the patient recovers from coma and the liver function approaches normal.

The effect on the blood and other soft tissues, as far as the concentration of glucose is concerned, is the same whether a given number of grams of glucose be removed by glycogenesis or by oxidation, and, inasmuch as a given quantity of insulin will ordinarily cause the disappearance of a given quantity of sugar, the degree of failure of glycogen storage may be expressed in terms of insulin deficit.

This is strikingly illustrated in columns 1 to 10 of table 5.

In column 1 the theoretical effect of 65 units of insulin should be to lower the blood sugar from 0.560 per cent (or from the theoretical peak of 1.310

per cent after administration of 100 gm. glucose) to 0.330 per cent. The actual result was 0.640 per cent, a difference above the expected result of 0.310 per cent. This can only mean that 0.31 per cent more glucose should have been oxidized or stored in the glycogen reservoirs by the given dose of insulin than actually happened. In terms of grams of glucose this excess which was not oxidized or stored approximates 41 gm. (0.0031 times the weight of the soft tissue). In terms of insulin this represents a deficit of 20 plus units.

The next nine columns illustrate what happens as the patient recovers from coma and the liver function (and possibly the pancreatic function) improve. The insulin deficit drops in succeeding columns.

In column 4 the blood sugar was 0.290 per cent. The patient was given 15 units of insulin, which theoretically should oxidize 30 gm. of glucose, causing a drop of 0.225 per cent with an expected blood sugar of 0.065 per cent. The actual result was 0.040, a difference below the expected level of 0.025 per cent, corresponding to a reduction of 3 gm. more glucose than calculated (total 33 gm.), indicating that the liver, or the pancreas, or both had begun to resume their functions in carbohydrate metabolism. This striking improvement in liver function occurred during the first 12 hours.

Here then, we have a measure of carbohydrate metabolism of great prognostic significance.

In columns 7, 8, 9 and 10 the patient was given 10-5-5 and 5 units of insulin respectively at 5:00 p.m.—8:00 p.m.—12:00 midnight and 4:00 a.m. She was given 53 gm. of glucose (as milk) in divided doses at 8:00 p.m.—12:00 midnight and 4:00 a.m. As indicated by the asterisks, blood sugars were not determined after 5:00 p.m. until the following morning. Theoretically, with the ingestion during the night of 53 gm. of glucose and the administration of 25 units of insulin the blood sugar should have been higher the following morning (0.235 per cent) than it was at the beginning (0.220 per cent). The actual result was a blood sugar of 0.040 per cent, a reduction of 0.195 per cent more than expected, or the equivalent of 26 gm. more glucose metabolized than anticipated. This is a very significant finding and can only indicate one or both of two things—namely that either the storage reservoirs took up some or all of this glucose or there was a production of approximately 13 units of endogenous insulin. Perhaps the liver and pancreas both shared in the disposal of the extra 26 gm. of glucose. At any rate, the improvement in carbohydrate metabolism is exactly the equivalent of, and may be expressed mathematically as, an insulin surplus of 13 units.

Columns 4 and 5 in table 5 furnish additional evidence that 1 unit of insulin metabolizes approximately 2 gm. of glucose. From midnight to 8:00 a.m. the endogenous insulin was calculated to be plus $1\frac{1}{2}$ units to minus $1\frac{1}{2}$ units, or practically zero.

If one unit of insulin will metabolize 2 gm. of glucose when the endogenous insulin equals zero, then 15 units exogenous insulin (column 4)

should metabolize 30 gm. of glucose, producing a drop in blood sugar of 0.225 per cent and a theoretical result of 0.065 per cent. The actual result was 0.040 per cent, a drop of 0.250 per cent, which corresponds to 33 plus gm. of glucose. If from this is subtracted 3 gm. metabolized by $1\frac{1}{2}$ units of endogenous insulin, the amount actually metabolized by the 15 units exogenous insulin was 30 gm.

In column 5 the patient received 76 gm. glucose and 25 units insulin. The theoretical effect of 76 gm. glucose (if the endogenous insulin equals zero) should be to raise the blood sugar from 0.040 per cent to 0.610 per cent. The effect of injecting 25 units insulin should be to metabolize 50 gm. of glucose, producing a drop of 0.375 per cent and a theoretical result of 0.235 per cent. The actual result was 0.260 per cent, a drop of 0.350 per cent, which corresponds to $46\frac{1}{2}$ gm. of glucose. If to this is added 3 gm.

TABLE VI
Case 2. Average Amounts of Endogenous Insulin Secreted

Date	a.m.	Noon	p.m.
12/5/38	-4 U	11 U	?
6	$24\frac{1}{2}$ U	19 U	?
7	27 U	14 U	?
8	21 U	?	?
9	32 U	26 U	?
10	37 U	29 U	10 U
11	34 U	39 U	13 U
12	28 U	?	?
13	35 U	35 U	11 U
14	35 U	?	14 U
15	36 U	25 U	20 U
16	35 U	29 U	20 U

not metabolized due to liver failure (endogenous insulin deficit), the amount actually metabolized by the 25 units exogenous insulin was $49\frac{1}{2}$ gm.

These results, as well as those in columns 9/22 and 9/23 in table 3 demonstrate the great accuracy with which insulin dosage can be calculated and the resultant blood sugars predicted if proper allowance is made for endogenous insulin.

It should be emphasized, however, that this cannot be done accurately during coma, but only when the patient has recovered to a point where the endogenous insulin becomes stabilized (see table 6). Then, with sufficient calculations to give an average estimate of liver and pancreatic equilibrium in terms of units of endogenous insulin, subsequent blood sugars should approximate very closely the theoretical calculations.

Table 6 presents in tabular form the calculated amounts of endogenous insulin surplus after breakfast, lunch and supper from December 5 to 16 inclusive.

Column a.m. shows an average endogenous secretion of 26 units of insulin in the morning on December 6, 7 and 8 (hospital days four, five and

six) followed by an increase to an average of 34 units in the morning thereafter for a period of eight days.

Column noon shows an average of 15 units secreted in the afternoon on December 5, 6 and 7, increasing to about 30 units average from December 9 to 16.

Column p.m. shows the average night secretion after the midnight insulin dose was discontinued and the patient was on three meals a day to be about 12 units from December 10 to 14 and 20 units on December 15 and 16.

SUMMARY

Hartmann² showed in 1925 how the insulin requirement may be calculated, given the blood sugar and the weight of the soft tissue. However, Hartmann's work did not take into account the factor of endogenous insulin secretion; and allowance for pancreatic function in figuring insulin dosage has been based upon guesswork and trial and error.

By an elaboration of Hartmann's method we have shown how the amount of insulin produced in the body may be estimated, and how, by subtracting the average number of calculated units of endogenous insulin from the total insulin requirement, we obtain an accurate estimate of the amount of exogenous insulin required. By this method we are able to compute with considerable accuracy the dosage of insulin necessary to lower the blood sugar any amount desired.

This is possible only after a sufficient number of calculations to strike an average, and cannot be done while the patient is in coma. We have shown how the failure of carbohydrate metabolism during coma, due to liver and pancreatic failure, may be expressed in terms of insulin deficit, and have indicated how this may be used as a prognostic aid and a guide to subsequent insulin dosage.

CONCLUSIONS

1. Proper insulin dosage can be calculated according to mathematical formulae.

2. The method of calculating insulin dosage described by Hartmann is incomplete because it does not take into account the variable factor of endogenous insulin.

3. It is possible by the method we have described to estimate the physiologic activity of the liver, pancreas and other organs concerned with carbohydrate metabolism in terms of units of endogenous insulin.

4. The exogenous insulin requirement may be calculated by this method more accurately than has heretofore been possible.

5. The blood sugar concentration may be predicted by our method with considerable accuracy following the administration of a definite amount of glucose and an exactly calculated dose of insulin.

6. Our calculations provide evidence that the conception that 1 unit of insulin will metabolize 2 grams of glucose is approximately correct.

7. The depression of carbohydrate metabolism due to liver and pancreatic failure during coma may be expressed mathematically in terms of insulin deficit.

8. The improvement in carbohydrate metabolism after recovery from coma may be estimated and mathematically expressed in terms of increasing amounts of endogenous insulin.

BIBLIOGRAPHY

1. SHARKEY, THOMAS P.: Diabetic coma, *Ohio State Med. Jr.*, 1936, xxxii, 123-130.
2. HARTMANN, ALEXIS F.: Diabetes mellitus in infants and children, *Med. Clin. North Am.*, 1925, ix, 69-99.

CLINICAL PICTURES ASSOCIATED WITH INCREASED BLOOD PRESSURE: A STUDY OF 100 PATIENTS *

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INTRODUCTION

UNTIL comparatively recently hypertension has been divided into the "renal" type (including glomerular nephritis and a few rarer disorders of the kidneys) and the "essential" type, the latter term being employed to indicate a rise in blood pressure not due to renal disease. Many clinicians have tended to accept essential hypertension as an entity due to a single but unknown cause. This concept is no longer tenable for two reasons. In the first place the demonstration by Goldblatt and his coworkers¹ that animals with experimental renal hypertension may present a clinical picture similar in all respects to that of essential hypertension in man has reopened the whole question of the distinction between renal and essential hypertension. In the second place there has accumulated during the past few years evidence which indicates that what was formerly called essential hypertension is not an entity, but is—like fever—a symptom which may be due to various causes. Some of these causes are known; others are entirely unknown; still others are partially known in the sense that they are suspected but their significance is unproved. Further knowledge in this field will appear more readily if the knowledge at present available can be sifted and classified. The purpose of this communication is to attempt a beginning toward the development of an etiologic classification of hypertension. Even though the evidence is much too incomplete to justify a final division of hypertension into various causes, a tentative division will perhaps be useful not only as a point of departure for a more accurate future classification but may also be of some immediate practical value in the treatment of patients.

In the discussion to follow no attempt will be made to review the extensive literature concerning hypertension. The report is concerned rather with a study of 100 patients having increased blood pressure. It will be shown that many of these patients fall into certain general groups, some of which are clearly defined, while others are still vague. Certain clinical features which require further study will be mentioned. Finally, an etiologic classification of hypertension which seems to be as accurate as can be developed in the present state of inadequate knowledge will be suggested.

* Read at the New Orleans meeting of the American College of Physicians March 28, 1939.

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This work was aided by grants from the Josiah Macy Jr. Foundation, the Rockefeller Foundation, and from Mr. Joe Werthan, Nashville, Tennessee.

SELECTION OF MATERIAL AND METHOD OF STUDY

The patients on whom this study is based have been observed either on the private wards or in the Out-Patient Department of the Vanderbilt Hospital. For the most part the study deals with cases seen consecutively. However, persons displaying elevation of the systolic pressure only and individuals with acute or chronic glomerulonephritis have been excluded. Furthermore, certain patients presenting unusual types of hypertension have been deliberately included for illustrative purposes, even though they did not fall within the consecutive series. All the patients dealt with have had at some time a systolic blood pressure of more than 150 mm. and a diastolic pressure of more than 100 mm. of mercury. In most of the individuals the elevation of blood pressure has been sustained but in a number the hypertension has been temporary.

All the patients have had complete histories and physical examinations, urinalyses, blood counts and determination of the non-protein nitrogen of the blood. Measurements of the rate of excretion of phenolsulphthalein, the concentrating power of the kidneys, the blood sugar and the basal metabolic rate were made in most instances. Glucose tolerance tests were done in many cases. At the beginning of the study the importance of the routine investigation of the urine for bacteria was not realized and this procedure was employed only when it seemed especially indicated. More recently cultures of the urine and in many instances search for bacteria in freshly voided urine have been made routinely. Measurements of the cholesterol content of the blood were made in a large percentage of the patients. Other diagnostic procedures have varied, depending on the indications in the individual subject.

After the findings in each patient had been summarized and tabulated an attempt was made to separate the cases into various syndromes. It should be pointed out again that such separation is not entirely justifiable at the present time and can only be defended on the grounds that it seems to us to represent the best that can be done in the present state of inadequate knowledge.

RESULTS OF CASE STUDIES

The chief findings are summarized in table 1.

A. The group as a whole exhibited few differences from similar groups studied by other authors. One somewhat surprising feature was the relative youthfulness of the patients. Our figure for the average age—49.3 years, indicated that most patients with increased blood pressure are middle-aged rather than elderly. Because of the method of selection of the patients, which involved the use of a large percentage of private patients, the figures relating to race have no significance. Our data indicating a preponderance of females over males in a ratio approximately 4:3 are practically identical with the findings of Fishberg.²

As regards the complications of hypertension the cerebral and cardiac manifestations were about equally frequent, the two most common symptoms being dyspnea and headache. If only serious manifestations are considered the phenomena dependent on cardiac disease were more frequent than those due to involvement of the nervous system. Although more than one-fifth

TABLE I
Summary of Clinical Manifestations on One Hundred Patients with Hypertension

	Neurogenic Group					Endo- crine Group	Metabolic Group		Renal Group						Congestive Heart Failure (Stagnant blood)	Mixed	Unclassified	Entire Group
	Psychoneurotic	"Stress and Strain"	Reflex (?)	Medullary	Increased Intra-cranial Pressure	Pituitary Basophilism	Menopause	Increased Blood Cholesterol	Increased Blood Uric Acid	Urinary Tract Obstruction	History of Stone, Colic or Hematuria	History of Pyelitis	Masked Pyelonephritis	Coarctation of Aorta				
Number of cases	6	5	2	2	1	10	10	7	3	8	8	5	8	1	2	5	17	100
Mean age	48	52	55	14	71	51	48	60	38	57	51	42	34	40	56	51	52	49.2
Sex { Male	3	3	2	1	1	7	0	3	2	3	4	1	1	1	1	2	9	44
Sex { Female	3	2	0	1	0	3	10	4	1	5	4	4	7	0	1	3	8	56
Previous { Hematuria	1(?)	0	0	0	0	0	0	1	0	0	3	0	1	0	0	1	1	8
Urinary { Renal stone or	0	0	0	0	0	0	0	0	0	1	6	0	0	0	0	1	0	8
Symptoms { colic	0	0	1	0	0	0	0	0	0	4	1	5	0	0	0	0	0	11
Others* { Pyelitis	0	0	0	0	0	0	1	1	1	4	0	5	8	0	0	4	5	29
Cerebral { Apoplexy and crises	0	3	0	0	0	5	4	2	1	1	3	0	0	0	0	2	4	25
Manifestations { Psychoneurosis	6	0	0	0	0	0	6	0	0	0	0	0	0	0	0	0	1	13
Others { Others	5	5	0	2	1	5	6	3	3	1	3	3	4	0	0	4	10	55
Cardiac { Angina pectoris	1	2	2	0	0	3	0	3	0	3	3	0	0	0	0	4	2	23
Symptoms { Limited reserve	1	1	2	0	0	5	3	1	3	3	3	1	2	0	0	2	6	33
Palpitation { Congestive failure	2	1	1	0	0	3	1	4	0	2	2	1	2	1	2	3	4	29
Palpitation { Palpitation	4	0	0	0	0	0	6	1	0	0	0	1	0	0	0	0	0	12
Vascular { Absent	6	2	2	2	1	6	9	6	3	7	5	2	6	1	2	2	11	73
Retinitis { Mild	0	1	0	0	0	4	1	1	1	0	3	1	1	0	0	2	3	18
Severe { Severe	0	2	0	0	0	0	0	0	0	0	0	2	1	0	0	1	3	9
Cardiac { Absent	2	1	1	2	1	4	5	3	1	1	3	2	2	0	0	0	4	32
Enlargement { Slight	2	3	1	0	0	6	4	3	2	3	2	1	4	0	0	1	8	40
Marked { Marked	2	1	0	0	0	0	1	1	0	4	3	2	2	1	2	4	5	28
Gallop Rhythm { Present	1	1	2	0	0	3	1	2	0	2	3	2	2	0	2	1	9	31
Absent { Absent	5	4	0	2	1	7	9	5	3	6	5	3	6	1	0	4	8	69
Blood Pressure { Highest	220	265	190	200	—	190	240	230	190	230	240	250	230	—	200	250	260	265
	120	180	110	140	—	120	135	140	124	130	130	170	170	—	120	150	160	180
	130	150	170	190	—	140	150	150	145	140	170	190	150	—	172	140	150	130
	90	100	150	98	—	100	100	90	95	90	95	110	110	—	110	100	98	90
Mean	164	218	180	195	170	177	201	195	162	182	196	219	185	160	186	205	206	194
	104	134	105	110	100	107	120	105	108	114	114	132	126	100	115	119	124	118

of the patients had had symptoms pointing toward cerebral vascular crises (hypertensive encephalopathy) at some time in the past, only 9 per cent had had "strokes." Twenty-three patients had angina pectoris while 30 per cent had had congestive heart failure at some time. (The term congestive heart failure as employed in this paper is used to designate not only patients with systemic congestion but also those individuals who in the absence of

systemic congestion had had pulmonary engorgement as revealed by a history of orthopnea, a history of paroxysmal dyspnea, or by physical signs.) The most common objective abnormality was cardiac enlargement (66 patients). Although gallop rhythm was observed in 28 instances, chronic

TABLE I (continued)

Summary of Clinical Manifestations on One Hundred Patients with Hypertension

	Neurogenic Group					Endocrine Group		Metabolic Group		Renal Group					Congestive Heart Failure (Stagnant shockdruck)	Mixed	Unclassified	Entire Group
	Psychoneurotic	"Stress and Strain"	Reflex (?)	Medullary	Increased Intracranial Pressure	Pituitary Basophilism	Menopausal	Increased Blood Cholesterol	Increased Blood Uric Acid	Urinary Tract Obstruction	History of Stone, Colic or Hematuria	History of Pyelitis	Masked Pyelonephritis	Coarctation of Aorta				
Renal Function { Normal Impaired	5 1	2 3	1 1	2 0	7 7	9 1	8 2	1 6	3 0	6 2	6 2	4 1	7 1	7 7	1 1	3 2	9 8	67 31
Urine { Albumin { present absent Fus† { present absent	0 0 0 6	2 0 0 5	1 1 1 1	0 0 0 2	0 0 0 1	2 1 1 9	0 8 0 10	4 10 0 7	0 3 0 3	1 3 0 4	2 6 4 4	1 4 1 4	0 8 1 7	1 0 0 1	2 0 0 2	3 2 2 3	8 9 2 15	27 73 16 84
	Blood Cholesterol { Number of observations Average value	4 159	1 167	0 —	0 —	5 160	6 201	7 257	2 182	1 200	4 188	2 189	5 143	0 —	1 178	1 208	4 170	43 186
	Leukocytosis** { Present Absent	0 6	3 2	1 1	2 0	1 0	0 10	1 9	2 5	0 3	4 4	3 5	1 4	4 4	0 1	1 5	0 13	4 73
	Anemia†† { Present Absent	0 6	0 5	0 2	1 1	0 1	0 10	4 6	0 7	0 3	2 6	0 8	3 2	2 6	0 1	0 5	0 15	2 86
Uremia { Present Absent	0 6	2 3	0 2	0 2	0 1	0 10	0 10	0 7	0 3	4 4	0 8	1 4	0 8	0 1	0 2	1 4	4 13	12 88
	Urine Cultures‡‡ { Not taken Sterile Colon bacillus Streptococci Other bacteria	3 3 0 0 0	2 1 0 1 2	1 0 0 0 1	2 0 0 0 0	1 0 0 0 0	6 2 1 0 0	3 7 1 0 0	3 2 0 2 0	1 2 0 0 0	1 1 2 2 1	1 2 0 2 2	0 0 2 3 0	— — — — —	1 1 0 0 0	1 2 0 2 0	1 6 1 5 3	4 29 13 24 9

* This does not include a history of gonorrhea and does not include frequency and nocturia except when very marked.

† This includes only cases in which palpitation was one of the main complaints and does not include palpitation associated with premature beats.

‡ This includes hemorrhage, exudate and papilledema.

§ In compiling the table only the average blood pressure for each patient was considered.

|| Renal function was considered as impaired when the maximum specific gravity as determined by Fishberg's procedure² was below 1.022 or the excretion of phenolsulphonephthalein was less than 50 per cent in two hours.

¶ Patients with only a few white blood cells per high power field were not included.

** This group included individuals with a leukocyte count of ten thousand or more.

†† Subjects with hemoglobin values of less than 12 grams per cent were classified as anemic.

‡‡ A few of the cultures were made directly from the ureters or on freshly voided specimens after carefully washing the genitalia, but most of them were catheterized specimens from the bladder.

auricular fibrillation was present in only two subjects. (We had expected to find a much higher instance of this arrhythmia.)

Although the cardiac and the cerebral disorders displayed by the patients were in the main the results of increase in blood pressure, the situation was quite otherwise in regard to the symptoms referable to the urinary organs.

In compiling the data we did not include those minor urinary symptoms such as mild degrees of polyuria, frequency and nocturia, which are so commonly the result of cardiovascular disease. Most of the patients did not have more serious urinary symptoms at the time of observation, but careful analysis of their histories revealed significant symptoms referable to the urinary tract in a fairly large percentage. Thus, 10 patients had had gross hematuria at some time in the past, seven individuals gave a typical story of renal colic, five subjects had had pyelitis. Five patients had either passed a kidney stone or had had a diagnosis of renal stone made at some time. Twenty patients had had in the past either dysuria, marked frequency of urination or both. In regard to these symptoms referable to the urinary tract, two points should be emphasized: First, that although quite definite they were not impressive and were not mentioned by the patients except in response to careful questioning; and second, these symptoms were of such a nature that they could not have been the result of hypertensive vascular disease. Whether or not such symptoms were in any way related to the causes of the hypertension will be discussed later.

Fifty-four of the 100 patients had a family history of some type of cardiovascular disease. Our histories in this regard were not particularly carefully taken and it is probable that the actual incidence of cardiovascular disease in the families of the hypertensive patients was considerably higher than this.

A note was made of the complexion in all cases. Twenty-eight subjects were ruddy and 17 were pale, the remaining individuals being normal in this respect. Most of our subjects did not therefore conform to either the red or the pale groups of Volhard.

The body habitus was recorded as thin (21 subjects), stocky (23 subjects), generalized obesity (15 subjects), obesity confined mainly or entirely to the trunk (11 subjects), or normal (29 subjects). Aside from that group of patients with a buffalo type of obesity these figures for the physical types are not particularly impressive and are probably not very different from what would be observed in a group of non-hypertensive patients with the same age distribution.

One interesting point was the rarity of anemia. No patient in the series had severe anemia and in only 14 instances was the hemoglobin less than 12 grams per cent. A leukocyte count of 10,000 per cubic millimeter or more was observed in 27 patients.

Pyuria (varying in degree from numerous white blood cells per high power field to clumps of white cells) was present in 19 instances. Many other patients showed occasional white blood cells which were not considered as significant.

Urine cultures were made in 68 patients. No bacteria were found in 31 instances. Positive cultures were obtained in the remainder. The significance of this finding will be discussed below.

Although when considered as a whole these 100 patients had little in common except increase in blood pressure plus a tendency toward symptoms brought about by the usual consequences of hypertension, a survey of the individual case records revealed a number of different clinical patterns, some of which were observed frequently while others occurred rarely. Granting that similarity in clinical features does not necessarily indicate identity in etiological background, these patterns seem to merit more detailed consideration.

B. *Syndromes Associated with Hypertension.* These fall into several groups, each with one or more subdivisions.

1. *Neurogenic.* This term is used to signify that the factors responsible for the increase in blood pressure appear to operate through the nervous system.* Five different subgroups were noted.

(a) *Psychoneurotic.* Six patients showed the clinical features of neurosis and resembled the cases described by Ayman.³ Anxiety was pronounced in each. Palpitation was the outstanding complaint in four subjects. Intermittent tachycardia was a striking feature. Superficially, the clinical features in these patients resembled those of thyrotoxicosis but all had normal metabolic rates. The blood pressure was much affected by emotion and showed marked decline with reassurance. Sedatives were especially beneficial in these subjects. The symptoms consisted mainly in palpitation and the usual symptoms of neurosis. However, cardiac enlargement was present in four patients. The blood pressure exhibited marked fluctuation according to the emotional state. Four of the six patients had a definite family history of hypertension.

These findings led us to suspect that in a person predisposed by heredity a severe and more or less continuous disturbance in the higher nervous centers may affect the sympathetic nervous system in such a way as to produce an increase in blood pressure, which, although at first intermittent, may later become permanent.† Granting that in cases such as these the psychoneurotic state is probably not the only etiologic factor, it is certainly an important one and therapy should be directed primarily toward it. That such therapy may at times be extraordinarily effective is illustrated by case 1. (See appended case records.)

(b) *"Stress and Strain."* Five patients displayed a syndrome resembling in some respects that of the previous group. Each of these individuals developed hypertension while living under conditions of unusual

* Such a statement does not imply that the rise in blood pressure is necessarily mediated through the vasoconstrictor nerves. Conceivably neurogenic hypertension could be induced through the effect of the nervous system on the endocrine glands, on the renal blood vessels, or by some unknown means. In this paper we are not concerned with the question of the exact mechanisms whereby the increase in blood pressure is produced but rather with the morbid states which set off or aggravate such mechanisms.

† A patient's knowledge that his blood pressure is increased frequently leads to the development of a psychoneurotic state. The problem as to which was primary in our cases could not be solved. From a practical point of view it makes no difference. The abnormal emotional state in these six patients was certainly an aggravating factor if not the primary cause and therapy directed toward it caused marked improvement.

mental and emotional strain. Three had hypertensive encephalopathy. Two developed malignant hypertension and died of uremia. Another subject who had severe symptoms (including a blood pressure of 300/200, cerebral crises and vascular retinitis), was diagnosed as malignant hypertension but improved markedly after the conditions responsible for the mental stress had been eliminated and two years later remains practically free of all symptoms with only moderate elevation of blood pressure.

Whether severe mental strain can initiate hypertension is debatable. In favor of an affirmative answer is the case of a 33-year old male (not included in the series) whose blood pressure was found to be 180/110 immediately after two weeks of intensive work under severe stress. When he reduced his working hours to 10 or 12 per day his blood pressure declined in a few days to 118/78. During repeated observations for 10 years before and for six years after this episode his blood pressure has always remained normal.

If it be assumed that a prolonged period of mental stress can produce elevation of blood pressure, one can best account for the development of malignant hypertension in some subjects within this group by assuming further that the increased blood pressure induces changes in the renal blood vessels, thereby causing further rise in blood pressure and inducing a vicious cycle.

Case 2 is illustrative of the condition which, for want of a better name, we have termed the "stress and strain" type of hypertension.

(c) *Reflex*. During anginal attacks the blood pressure is usually elevated. This is not simply a result of pain for Levine and Ernstene⁴ showed that severe pain due to other causes was not attended by a similar rise in blood pressure. Alam and Smirk⁵ found that exercising ischemic skeletal muscles caused a well marked increase in blood pressure which set in before pain occurred. The effect was apparently of reflex nature because under the conditions of the experiments the venous return from the ischemic muscular tissue was blocked. One occasionally observes patients with hypertension who, following coronary thrombosis and disappearance of the previous anginal attacks, have a normal blood pressure for months or years. (We are not referring here to the acute decline in blood pressure during the first few days but to the persistent decline, which remains after the patient has recovered entirely.) In our series of 100 hypertensive individuals there were two such patients. One of them was of especial interest because his blood pressure had been followed for a number of years and had not become elevated until he developed angina pectoris. Following myocardial infarction he had no more anginal attacks and his blood pressure has remained within normal limits for 18 months since.

The facts mentioned in the preceding paragraph can be accounted for if one assumes that an ischemic area in the heart may cause a reflex rise in blood pressure. Against such an assumption are the following points:

(1) Many patients with angina pectoris do not have hypertension.

(2) A reflex rise in blood pressure induced by oxygen deficiency in the heart has not to our knowledge been demonstrated in experimental animals. The evidence that sustained hypertension may be brought about by a reflex from the heart is therefore entirely inconclusive. Even if such a mechanism does exist, this type of hypertension will remain difficult to recognize because it can only be diagnosed in patients whose blood pressures have been followed before and after coronary thrombosis. We are certainly not justified in assuming that this mechanism is operative in all patients who have sustained increase in blood pressure and are subject to attacks of angina pectoris, because the latter disorder is of fairly frequent occurrence in patients with any type of hypertension.

An instance of hypertension which may conceivably have been due to reflex from the heart is illustrated by case 3.

(d) *Medullary.* Certain disorders which cause injury to the brain stem may be accompanied by hypertension. Such was the case in two of our patients. One was a boy of 20 with acute poliomyelitis and a blood pressure of 200/92 (case 4). We have likewise observed two patients with post-diphtheritic paralysis whose blood pressures were elevated and declined to normal as the paralysis disappeared (cases 5 and 6). Whether in such instances the hypertension is brought about directly, through irritation of the vasomotor centers and the brain stem, or whether some other mechanism is concerned is uncertain.

(e) *Increased Intracranial Pressure.* One patient in our series had an elevation of blood pressure associated with a skull fracture. Such cases are quite common. Less frequently conditions which cause more persistent elevation of the intracranial pressure may induce hypertension. Occasionally a vicious cycle is set off, hypertension induced by any means leading to increased intracranial pressure, and this in turn causes further rise in blood pressure. The dramatically beneficial results of spinal puncture in certain patients with eclampsia can probably be ascribed to the breaking up of such a cycle.

2. *Endocrine Group.*

(a) *Pituitary.* Ten of the 100 patients presented features suggestive of pituitary basophilia (Cushing^o). Each of the individuals had obesity involving the trunk with relatively slender extremities. Each had a florid complexion and a short neck. Four subjects had hyperglycemia, three had skeletal decalcification and one had sciatica. Seven of the 10 subjects were males. None of the patients had malignant hypertension. Although symptoms referable to the heart and brain were common there was no history of symptoms referable to the kidneys. As a rule both the systolic and diastolic pressures were less elevated than in most of the other groups. Of four patients treated with deep roentgent-ray therapy over the pituitary gland only one showed marked improvement (case 7). On theoretical

grounds it would seem that reduction of weight should have an especially beneficial action in obese patients with pituitary hypertension for there is reason to believe that restriction in caloric intake may depress the activity of the basophilic cells of the anterior lobe of the hypophysis.

(b) *Menopausal*. Ten subjects were included in this group because their increase in blood pressure set in concurrently with the onset of the menopause. The relationship of the increase in blood pressure to the cessation of menstruation seemed fairly definite in three patients who exhibited rise in blood pressure following induction of the menopause by artificial means. However, of the seven patients with hypertension developed at the time of spontaneous menopause, six were definitely psychoneurotic and the increase in blood pressure in these subjects could just as readily have been ascribed to this factor as to the menopause. When considered as a whole this group was characterized by the absence of retinal changes, the frequency of palpitation, the occurrence of anemia—a symptom which was quite unusual in most of the hypertensive patients—and a relatively mild course. Prolonged treatment of two patients who were not psychoneurotic with large doses of the female sex hormone was without effect on the blood pressure. However, the patients in this group who are psychoneurotic are usually benefited by relieving their symptoms by sedation or substitution therapy.

3. *Metabolic Group*.

(a) *Increased Blood Cholesterol*. In seven patients the only abnormality found which could reasonably be related to the genesis of the hypertension was increase in blood cholesterol. These patients were somewhat older than those in the other groups; angina pectoris was frequent; general arteriosclerosis was outspoken; congestive heart failure was common; the pulse pressure was relatively high; the aortic knob was prominent in fluoroscopic examination. These points led to the suspicion that the increase in blood pressure in these patients might have been the result of atheroma of the renal arteries with consequent impairment of the renal blood flow and the induction of a mechanism corresponding to that responsible for the experimental hypertension caused by artificial narrowing of the renal arteries (Goldblatt, et al.¹). The findings in the only patient within this group who was subjected to necropsy were compatible with this view (case 8). Four of the patients in this group had diabetes, two had hypothyroidism. In view of the possible relationship of the increase in the blood cholesterol to the genesis of the hypertension it would be of interest to observe the effect of the administration of thyroid to the patients. We have not as yet made any observations on this point.*

(b) *Increased Blood Uric Acid*. One patient had outspoken gout with well marked elevation of blood uric acid. Two other subjects had slight

* Since this paper was written we have observed a number of additional patients with hypertension, hypercholesterolemia, and evidence of arteriosclerosis. It seems probable that sclerosis of the larger renal arteries is the most common cause of hypertension developing after the age of fifty-five.

elevations of the uric acid content of the blood without other signs of gout. Whether the increase in blood pressure in these three patients could have been related to uric acid deposits in the kidneys is uncertain.

4. *Renal Group.* Thirty patients had evidence pointing toward some type of kidney disease either at the time of observation or in the past. These subjects were divided into five sub-groups:

(a) *Urinary Tract Obstruction.* Of the five females in this sub-group one had a carcinoma of the ovary, one had ovarian cyst, two had uterine myomata and one had had a stricture of the ureter several years previously. Of the three males one had benign hypertrophy of the prostate, a second had urethral stricture and later developed carcinoma of the prostate, and a third had chronic prostatitis. The average age of the eight patients was 55 years. Four of the subjects had pyuria during observation. Anemia was present in three instances and leukocytosis in four. The hypertension was relatively mild and none of these eight subjects had evidence of malignant hypertension. Vascular retinitis was present in only one individual and was mild in this patient. Urine cultures were positive in five of the six instances in which they were made, the chief organisms being the colon bacillus and a streptococcus. Eradication of the infection with sulfanilamide was followed by marked decline in blood pressure in one patient (case 9), and questionable benefit in the only other subject in whom this procedure was carried out.

Four of the patients with urinary tract obstruction had nitrogen retention. These were the only instances in the entire series of 100 hypertensive patients in which renal insufficiency occurred in conjunction with relatively little hypertension. All of the other subjects with uremia had a more marked elevation. This point may possibly be of some diagnostic value.

Only one of the patients in this sub-group died while in the hospital. The autopsy finding of marked unilateral pyelonephritis furnished strong evidence for the view that the urinary tract obstruction was responsible for the elevation of blood pressure (case 10).

(b) *History of Stone, Colic or Hematuria.* Of the eight patients in this sub-group six had a typical history of renal colic and three had had unexplained hematuria at some time in the past. There were four males and four females, the average being 51 years. Vascular retinitis of mild degree was present in three patients but none had severe retinitis. The increase in blood pressure was relatively mild, there being no instances of malignant hypertension. At the time of observation four of the patients had pyuria and three had leukocytosis. The pyelograms were abnormal in two of the three instances in which they were made. None of the subjects had nitrogen retention. Urine cultures were positive in five of the seven patients, showing colon bacillus in two cases, streptococcus in two and staphylococcus once. Attempts to disinfect the urinary tract were not made in any of the patients.

(c) *A typical history of pyelitis* was given by five subjects, four of them

being females. In two of the patients the pyelitis began during pregnancy. The average age in this sub-group was relatively low, being 42 years. Vascular retinitis was absent twice, mild in one patient and severe in two others. The latter two subjects had malignant hypertension. Renal function was impaired in only one of the five patients, this individual later dying of uremia. Albumin was absent from the urine of four of the five subjects and pus was found in the urine at the time of observation in only one instance. Three of the five patients were anemic. Urine cultures were positive in each of the four subjects in which they were made. Colon bacilli were found three times, streptococci three times and staphylococci once. Attempts to disinfect the urinary tract were not made. (Case 11 represents an example of hypertension occurring in a patient with a history of pyelitis.)

Peters⁷ has recently pointed out the importance of pyelitis in relation to the so-called toxemias of pregnancy. The correctness of his view that a relationship exists between these disorders is supported by two of our patients who had pyelitis during pregnancy and who developed increase in blood pressure at this time. Both of these individuals were originally diagnosed as having "toxemia of pregnancy." The findings in the other three patients in the group suggest that the occurrence of hypertension in association with pyelitis is by no means limited to pregnancy. The situation in regard to these five patients may be summarized by saying that they had "burnt out" pyelitis masquerading as "essential" hypertension.

(d) *Masked Pyelonephritis*. This term is applied to eight young subjects with an average age of 34 years, of whom seven were females, who presented a picture somewhat similar to that described by Longcope,⁸ but differing from that of his subjects in that the symptom-complex simulated "essential" hypertension rather than chronic glomerular nephritis. These patients differed from those in the previous sub-group in that they did not give a definite history of pyelitis. The symptoms were vague and mild. Five of them complained of mild pain in the back which usually appeared with fatigue in the latter part of the day. Four of them had had either frequency, burning or nocturia at some time in the past but these symptoms had not been pronounced and were usually mentioned only in response to careful questioning. Only one of the eight subjects had had hematuria. The increase in blood pressure had been discovered accidentally in most of the subjects. Cerebral symptoms were either absent or of minimal severity. None of the eight patients had angina pectoris, although four had some cardiac enlargement, two had dyspnea on exertion and two had congestive heart failure. Vascular retinitis was present in two subjects and severe in one of these who had the typical picture of malignant hypertension. Albumin was absent from the urine in all instances. The initial routine examination of the urine showed pyuria in only one case, but repeated examinations of catheterized specimens revealed occasional clumps of white blood cells in most of the others. These patients tended to have

an intermittent slight fever. Mild anemia occurred in two of the eight subjects while four had leukocytosis. Nitrogen retention was absent in all instances. Pyelograms were made in four patients and all were either abnormal or revealed changes of doubtful significance. Urine cultures yielded streptococci in six patients and colon bacilli in the other two.* Attempts at disinfection of the urine were made in five instances. Distinct benefit was observed twice and questionable benefit in the remaining three subjects. The two patients who seemed to be improved the most are illustrated by cases 12 and 13. Our limited experience up to the present time does not justify any conclusions as to the value of therapy of this type. Conceivably the decline in blood pressure observed may have been coincidental. It is also possible that more prolonged and more intensive therapy might be beneficial in a larger percentage of the cases. These questions are still under investigation.

(e) *One patient had coarctation of the aorta.* He has been classified in the renal group because the investigations of Rytand⁹ have shown that experimental narrowing of the aorta above the level of the renal arteries causes hypertension, while the same procedure carried out immediately below the renal arteries produces no rise in blood pressure. Rytand also showed that hypertension could be produced by constricting the aorta between the renal arteries. If the lower kidney was removed the animals did not develop hypertension. His observations seem to indicate that the mechanism described by Goldblatt is responsible for the increase in blood pressure which occurs in the upper part of the body in patients with coarctation of the aorta.

These observations concerning the frequency of renal disorders in patients with "essential" hypertension are in accord with the studies of Schroeder and Steele,¹⁰ who found that a large percentage of hypertensive patients had abnormal pyelograms.

5. *Congestive Heart Failure.* Although cardiac decompensation, when setting in acutely, is usually accompanied by hypotension, an increase in blood pressure frequently occurs when heart failure develops slowly. In such instances the blood pressure declines as improvement occurs. The mechanism of this increase in blood pressure (*Stauungshochdruck*), which appears in certain patients with congestive heart failure is unknown. Various possible factors have been discussed elsewhere.¹¹

In two of our 100 hypertensive patients the blood pressure declined to normal as improvement in the cardiac condition occurred. No cause—

* In the absence of gross infection urine cultures must be very carefully evaluated. Voided urines collected under aseptic conditions in normal men yield organisms in over half the cases, which bacteria are apparently normal inhabitants of the anterior urethra. Catheterized urine from both men and women may contain bacteria although infection does not exist. To be certain that infection is present in the kidney one should grow bacteria from urine obtained directly from the kidney. Demonstration of the organism by direct smear is of definite aid in diagnosis. Since the concentration of urea in urine is often high enough to be bacteriostatic one should always inoculate the media directly after obtaining the specimen. Streptococci which occur in the urine are often partially anaerobic and grow better in poured blood plates or anaerobic broth.

other than congestive failure—for the hypertension could be found in either subject. Several other patients who were classified in other groups displayed decrease in blood pressure—but not to normal levels—as heart failure disappeared. It would seem that cardiac decompensation is frequently an aggravating cause of hypertension but is only occasionally the primary factor.

6. *Mixed Group.* Many of the patients who were considered as belonging to the various groups which have been discussed had evidence of more than one cause for the increase in blood pressure. In most instances one factor seemed to be the chief one and the subjects were classified accordingly. There were four patients who displayed more than one possible cause of the increase in blood pressure without predominancy of any particular factor. One other patient (case 6) developed hypertension in association with post-diphtheritic paralysis. Several months after her blood pressure had returned to normal she developed acute pyelonephritis and associated with this her blood pressure again became elevated. These subjects were placed in the “mixed” group.

7. *Unclassified Group.* As has been mentioned, the purpose of this study was to attempt a beginning at the development of an etiologic approach to the problem of hypertension. Consequently, an effort was made to classify each patient according to some factor which might conceivably be responsible for the increase in blood pressure, even though we realized clearly that the evidence justifying such a classification was decidedly inadequate. Even when rather elastic criteria were used there were still 17 patients who could not be classified. If we had adhered to rigid criteria and had insisted that no patient be placed in a group unless the cause of the increase in blood pressure was clearly established, the unclassified group would have been much larger and would have included most of the patients.

DISCUSSION

On the basis of the data which have been presented, of our experience with other hypertensive patients which were not included in the present series, and of reports in the literature, the following classification of hypertension is suggested as representing a working approach toward an etiological concept of this disorder:

CLASSIFICATION OF HYPERTENSION *

I. Neurogenic

A. Psychogenic

1. Psychoneurotic †
2. Stress and strain

* This does not include patients with elevation of the systolic pressure only.

† These conditions are likely causes of elevated blood pressure in children or young adults.

B. Medullary

1. Diphtheria †
2. Poliomyelitis †
3. Encephalitis †

C. Increased intracranial pressure †

D. Reflex

1. Carotid sinus ‡
2. Aortic depressor nerves ‡
3. Ischemic muscle
 - a. Cardiac
 - b. Skeletal

II. Endocrine

A. Pituitary (basophilic hyperplasia—Cushing's syndrome)

B. Adrenal

1. Medullary—adrenalin (pheochromocytoma) ‡
2. Cortical tumors

C. Ovarian

1. Menopause
2. Arrhenoblastoma

III. Renal

1. Acute and chronic glomerular nephritis †
2. Obstruction to urine flow †
 - (a) Congenital anomalies †
 - (b) Ureteral stricture †
 - (c) Urethral obstruction
 - (d) Pelvic tumors
 - (e) "Spinal" bladder
3. Urinary tract infection
 - (a) Pyelitis †
 - (b) Pyelonephritis (classical or masked) †
4. Diseases of renal arteries
 - (a) Renal atheroma (large and small arteries)
 - (b) Arteriolar sclerosis §
 - (c) Infarcts of kidney
5. Tumors of kidney
 - (a) Wilms tumor †
 - (b) Other tumors

* Prinzmetal and Oppenheimer¹² showed that the gradient between the pressures in the brachial and digital arteries is abnormally great in hypertension of this type because adrenalin causes constriction of the medium sized arteries.

† These conditions are likely causes of elevated blood pressure in children or young adults.

‡ Demonstrated in animals but not in man.

§ Although arteriolar sclerosis is probably initiated by hypertension in most instances it tends to cause a further rise in blood pressure.

6. Coarctation of aorta ‡ (see footnote on previous page)

7. Renal calculi

IV. Metabolic

1. Hypercholesterolemia (renal atheroma?)

2. Gout (uric acid deposits in kidneys?)

V. Congestive heart failure

VI. Mixed and unclassified causes of hypertension

In regard to this classification certain points should be emphasized:

(1) No attempt has been made to distinguish between underlying and aggravating causes of hypertension. Thus, glomerular nephritis is clearly an underlying cause, while mental stress and strain is in all probability an aggravating or precipitating cause. Many of the conditions which have been listed seem to produce hypertension only when they occur in predisposed subjects. Thus, mild renal infections seem to cause hypertension in some patients while more severe renal infections in other subjects may be accompanied by normal blood pressure. The difference may be ascribed to "predisposition," but this is simply substituting a name for an explanation, for we do not know what predisposition is, although we assume that it operates in some way through heredity. Until more is known about this question it seems wise to include in an etiological classification all factors which seem to produce hypertension, even though some of them may not initiate the disorder but serve only to intensify it. In this paper interest is centered primarily on those etiological factors which can be treated, and from this standpoint it makes no difference whether a given condition is underlying or aggravating, provided that treatment directed toward it will produce benefit.

(2) The classification which we are suggesting is concerned with conditions tending to lead to hypertension but does not deal with the mechanism whereby the increase in blood pressure is brought about. In spite of the important advances made within the past few years, the pathogenesis of hypertension remains obscure in many patients. There is some evidence that what we have called neurogenic hypertension may actually operate through the kidney. Thus, Braun¹³ found that the experimental hypertension produced by the intracisternal injection of kaolin can be alleviated by renal denervation. It is also likely that most types of endocrine hypertension may operate through some renal mechanism for it has been shown that integrity of the adrenal cortex is necessary in order to produce hypertension by means of renal ischemia (Goldblatt,¹⁴ Blalock and Levy¹⁵). Another unsolved problem relates to the means whereby obstruction and infection in the urinary tract induce a rise in blood pressure. The question as to whether such conditions act through interference with blood supply to the kidney is still unanswered. At the present time no final conclusion can be drawn concerning the exact mechanism of the various types of renal hypertension,

or regarding the possible relationship of extra-renal hypertension to renal pressor mechanisms.

(3) In the classification mentioned above reference to the toxemias of pregnancy has been deliberately omitted. Peters⁷ has shown that a large percentage of such patients have pyelitis. Even in the absence of infection it is probable that hydronephrosis due to pressure on the ureters from the enlarged uterus may induce a rise in blood pressure. In still other instances pregnancy may occur in a woman already having chronic glomerular nephritis or some other cause of hypertension. Whether endocrine disturbances play a rôle in the production of hypertension during pregnancy is still unknown. Until further evidence is available it seems wise to regard hypertension during pregnancy not as a disease entity but as similar in origin to hypertension appearing in non-pregnant individuals, modified and often intensified by pregnancy.

(4) Increase in blood pressure is especially important when it appears in children and young adults. In such subjects there is less apt to be serious damage to vital structures, and hence more permanent benefit can be produced if the cause of hypertension can be removed. The following conditions are especially likely causes of hypertension occurring under the age of 30: psychoneurosis; injury to the brain stem from diphtheria, poliomyelitis or encephalitis; tumors of the adrenals, medullary or cortical; acute and chronic glomerular nephritis; pregnancy, ureteral stricture and other conditions causing urinary tract obstruction; pyelitis and pyelonephritis; Wilms tumor of the kidney and coarctation of the aorta. In young hypertensive subjects these conditions should be looked for and an especially careful search should be made for masked infections in the kidney, for urinary tract obstruction and for tumors of the kidney or adrenal glands, because these conditions are particularly amenable to therapy.

(5) Is malignant hypertension a disease entity? Our observations, while not entirely conclusive, suggest a negative answer to this question. Of the 100 patients with increased blood pressure nine had typical malignant hypertension. Two of these, both males, were classified as belonging to the stress and strain group because their hypertension was known to have developed during prolonged and severe business stress associated with unusually hard mental work. Three patients, all females, with typical malignant hypertension, had pyelitis or pyelonephritis, the vascular lesions apparently developing secondarily as the result of hypertension induced by the renal infection. A sixth patient had some of the manifestations of pituitary basophilia, had been under unusually severe business strain and had three positive urine cultures for streptococci. He was classified in the mixed group. In the other three patients with malignant hypertension no apparent etiological factors could be found and the nature of their hypertension was not classified. Until more conclusive evidence is available it seems best not to consider malignant hypertension as an etiological entity. Apparently, it represents a severe reaction in the renal arterioles to increase in blood

pressure. Presumably the stimulus responsible for hypertension causes unusually marked vasoconstriction in the afferent glomerular vessels of some especially predisposed young subjects. Such vasoconstriction apparently leads to injury to the vessel wall with narrowing of the lumen. The renal ischemia so induced causes further hypertension, which in turn aggravates the renal vasospasm. The progressive vicious cycle so brought about seems to be responsible for the clinical picture designated as malignant hypertension. Such a concept accounts for the rapid appearance of malignant hypertension in persons who have previously had the picture of benign hypertension. If it be assumed that malignant hypertension is an entity, instances of this type have to be ascribed to coincidence of two different diseases, both of which can elevate the blood pressure.

The purpose of this communication has been to point out that a considerable body of knowledge is available concerning the conditions responsible for hypertension. Even though this knowledge is as yet far from complete, that portion of it which is at hand can be utilized. The underlying factors responsible for increase in blood pressure can be determined in some cases and important aggravating factors can be found in the great majority of cases. By recognizing and treating such factors much can be accomplished in the alleviation of that important group of disorders which are characterized by hypertension

SUMMARY

A study has been made of 100 patients with increase in blood pressure in an attempt to classify them according to conditions playing a rôle in the production of the hypertension. Although it has not been possible to distinguish with certainty between underlying and aggravating causes of hypertension, and although in many of the patients more than one factor has seemed to be of importance, most of the individuals have displayed one major condition which appeared to be the most significant cause of the rise in blood pressure. The patients have been classified as follows:

(1) *Neurogenic Group* (16 cases). This included six psychoneurotic subjects, five other patients who were living under unusually severe conditions of mental stress when the hypertension appeared, two patients in which the hypertension disappeared permanently after coronary thrombosis and in whom it is thought that the increase in blood pressure may have been of reflex origin from the heart, two patients with acute diseases involving the brain stem and one subject with increased intracranial pressure as the result of skull fracture.

(2) *Endocrine Group* (20 cases). This included 10 subjects presenting evidence of basophilic hyperplasia of the pituitary gland, and 10 women in whom the onset of hypertension coincided with the menopause.

(3) *Metabolic Group* (10 cases). This included seven patients with hypercholesterolemia who were suspected of having atheroma of the large

renal vessels and three patients with increased blood uric acid. In the latter subjects urate deposits in the kidneys were thought of as possible causes of the hypertension.

(4) *Renal Group* (30 cases). This included eight subjects with obstruction to the urinary tract, eight patients with a history of stone, colic or hematuria, one patient with coarctation of the aorta, five patients with a history of pyelitis and eight subjects with evidence of masked pyelonephritis. In the two latter sub-groups evidence of renal infection was often minimal and was obtained only by unusually thorough examination.

(5) *Heart Failure Group* (2 cases). Both of these individuals had hypertension during congestive heart failure, the blood pressure returning to normal and remaining at a relatively normal level following improvement in the cardiac condition.

(6) *Mixed Group* (5 patients). These individuals had evidence of more than one of the conditions which have already been mentioned, no single factor seeming to be more important than the others.

(7) *Unclassified Group* (17 cases). In these subjects no definite condition which might have been responsible for the increase in blood pressure could be determined.

It has been pointed out that whereas in some of these groups no effective therapy is available, in other groups the conditions which are apparently responsible for the increase in blood pressure can be markedly benefited provided that such conditions are recognized by careful studies of the individual patient.

CASE REPORTS

Case 1. P. G., a 27-year old white male, became ill nine months before admission, following the death of his father from angina pectoris. He developed a marked cardiac neurosis with hypertension and tachycardia. History otherwise was negative. The only positive physical finding was a blood pressure of 186/106. Laboratory findings were all negative. Under evipal anesthesia the blood pressure declined to 130/80 and then returned to the previous level. There was no significant fall in pressure during a six-week period of bed rest in the hospital. The blood pressure decreased to normal levels after psychotherapy and has not been recorded above 140/80 during the year following admission.

Case 2. C. F. N., a 57-year old white male, had had his blood pressure taken frequently during yearly physical examinations. In 1933 he had difficulties in his business and in addition to working for long hours under severe mental stress, finally lost his business to the bank. At this time he began to have severe headaches and his blood pressure which had previously been normal was found to be elevated. Subsequently, he had a typical attack of hypertensive encephalopathy. He became very depressed and anxious about himself. He then obtained a position which gave him reasonable economic security but allowed him to lead a restricted life. The blood pressure declined rapidly from the previous systolic level of 220 to 160-180.

On admission to the hospital the blood pressure was 180/100. Following reassurance, mild sedation and 24 hours rest in bed it declined to 124/80. After resuming his usual activities he remained free of symptoms for several weeks. The subsequent course is unknown.

Case 3. A. J., a 66-year old white male, who had been under observation for several years, had always had a normal blood pressure until he developed angina pectoris. For several months, during which he was having frequent attacks of pain, the blood pressure ranged from 190/120 to 172/100. He then had coronary thrombosis with marked circulatory collapse and was almost moribund for several days. During the 18 months since recovery the blood pressure has been taken on numerous occasions and has usually been 120-130/80-95. The highest pressure observed since coronary thrombosis was 150/100. He remains free of angina pectoris and has no symptoms of diminished cardiac reserve.

Case 4. W. G., a 20-year old boy, entered the hospital with acute anterior poliomyelitis of the spinal cord and brain stem. History and examination were negative except for signs of poliomyelitis and hypertension (200/92). Postmortem examination confirmed the diagnosis of poliomyelitis and was otherwise negative.

Case 5. S. C., an 8-year old girl, entered the hospital with tonsillar and pharyngeal diphtheria. The blood pressure on admission was 120/80. As the acute symptoms and fever subsided she developed cranial nerve palsies. Associated with this her blood pressure rose gradually to 190/138 and then as signs of paralysis cleared returned to a normal level—110/70—where it has remained. The urine was at all times essentially negative.

Case 6. A. N., a 40-year old white female, was first seen with post-diphtheritic paralysis and bulbar symptoms. Her blood pressure at this time was 150/110. The urine was negative at this time. As the bulbar symptoms cleared the blood pressure decreased to normal and remained so for about a year, when she began to have some back pain and intermittent chilly sensations. At this time her urine contained abundant pus and her blood pressure remains elevated.

Case 7. E. H., a white female, aged 37, complained of headaches and weakness. These symptoms had been present for two years during which time menstruation had been irregular and scanty. Both parents had died of hypertension. She was 63 inches tall and weighed 191 pounds. The obesity involved the arms and thighs somewhat but was mainly confined to the trunk, especially the abdomen. The neck was quite short, the complexion was ruddy, the blood pressure varied between 180-200/105-110. There were a few plum colored striae over the abdomen. The fasting blood sugar was normal but there was an abnormally pronounced and prolonged rise in the blood sugar curve following the administration of glucose. Following a course of deep roentgen-ray therapy over the pituitary gland the subjective manifestations disappeared and the blood pressure gradually declined to 130/70. During the next three months the blood pressure was measured repeatedly and the highest value found was 150/90.

Case 8. E. G. was a 47-year old white male who had many complaints. He was found to have myxedema, peripheral neuritis due to vitamin B₁ deficiency and severe hypertension. He had a history of having passed bloody urine on several occasions. There was no history of urinary tract infection. On examination his urine was at times negative and at times showed albumin, red cells and casts. The blood pressure was 230/140. The blood cholesterol was 333. He developed a dissecting aneurysm of the aorta and died. At autopsy the kidneys showed many old healed infarcts, marked large vessel arteriosclerosis and moderate arteriolar sclerosis.

Case 9. L. B., a 72-year old negro male, was first seen in 1933 with an enlarged prostate and a blood pressure of 140/90. Prostatectomy was done and a microscopic diagnosis of adenocarcinoma made. He developed *B. coli* urinary tract infection. The blood pressure gradually rose during the following years and from 1935 until readmission to the hospital ranged between 180/110 and 230/130. When examined in the hospital the findings were those of a chronic cystitis and pyelonephritis with a *B. coli* infection. He was treated with sulfanilamide. The urine cleared up in nine days. His blood pressure remained up during his stay in the hospital but two

weeks after discharge it was 130/90, and the following week and for two months since then has remained within normal limits.

Case 10. M. F. J., a 45-year old Negress, has been followed for 10 years because of chronic heart failure due to rheumatic heart disease with mitral stenosis and insufficiency. Gradually during the last eight years she has developed increase in blood pressure. During this time she has had a markedly enlarged uterus due to myoma. She has had no urinary symptoms. The urine contained varying amounts of albumin, a few white cells and occasional casts. Urine cultures were positive for *B. coli*. At autopsy the left kidney was markedly contracted and displayed the typical changes of advanced pyelonephritis with dilatation of the ureter secondary to pressure from the myoma. The right kidney was normal except for early granular changes in the cortex and slight changes in the vessels.

Case 11. C. S., a 34-year old white female, was first seen in 1931. She had a history of pyelitis appearing during pregnancy seven years previously. Since that time there had been occasional attacks of frequency and burning and she had been treated by a urologist for cystitis and pyelitis. The blood pressure in 1931 was 160/100. The urine showed a trace of albumin and there were 10-15 white blood cells per high powered field in the centrifuged specimen. She was not seen again until 1938. During the interval she had continued to have occasional attacks of frequency and burning on urination but these symptoms had not been pronounced. Examination in 1938 revealed marked contraction of the retinal arteries and early papilledema. The blood pressure was 264/148, and there was well marked cardiac hypertrophy. Intravenous and retrograde pyelograms showed dilatation of the left ureter and of the pelvis of the left kidney. The urine contained a moderate amount of albumin but only rare white blood cells. However, specimens obtained from the two kidneys by ureteral catheter each showed a few clumps of white blood cells and numerous gram negative bacilli. Repeated urine cultures were positive for colon bacilli.

Case 12. M. L., a 25-year old Negress, was first found to have elevated blood pressure in 1934 during a routine examination. For several years she had noted mild back pain associated with fatigue. When seen in 1939 she was four months pregnant and the blood pressure was 175/110, the examination being otherwise negative. The catheterized urine showed a few red blood cells, very rare clumps of white blood cells and streptococci. Cultures showed streptococci. Pyelograms revealed slight bilateral dilatation. During three weeks in the hospital her blood pressure averaged 160/120. She was treated with sulfanilamide. The infection was cleared up and her pressure subsequently dropped to normal where it has remained throughout her pregnancy and for four months since delivery.

Case 13. S. L., a 33-year old white female, complained of blurring and loss of vision and some urinary symptoms which consisted of periods of burning and frequency. During such periods she had at times slight facial edema. She was admitted to the hospital and was suspected of having a brain tumor because of marked choking of the discs. An exploratory craniotomy was done. This was negative. The urine was negative except for a few white blood cells. Culture showed streptococci on many occasions. After a period of three weeks in the hospital, during which time the blood pressure averaged about 170/120, she was treated with sulfanilamide. The infection subsided, the blood pressure dropping to normal, where it remained the following year.

BIBLIOGRAPHY

1. GOLDBLATT, H., LYNCH, J., HANZAL, R. F., and SUMMERVILLE, W. W.: Studies on experimental hypertension; production of persistent elevation of systolic blood pressure by means of renal ischemia, Jr. *Exper. Med.*, 1934, lix, 347.

2. FISHBERG, A. M.: Hypertension and nephritis, 1931, Lea & Febiger, Philadelphia, p. 668.
3. AYMAN, D.: Personality type of patients with arteriolar essential hypertension, *Am. Jr. Med. Sci.*, 1933, clxxxvi, 213.
4. LEVINE, S. A., and ERNSTENE, A. C.: Observations on arterial blood pressure during attacks of angina pectoris, *Am. Heart Jr.*, 1933, viii, 323.
5. ALAM, M., and SMIRK, F. H.: Observations in man upon blood pressure raising reflex arising from voluntary muscles, *Jr. Physiol.*, 1937, lxxxix, 372.
6. CUSHING, H. W.: Papers relating to the pituitary body, hypothalamus and parasympathetic nervous system, 1932, Thomas & Co., Springfield.
7. PETERS, J. P.: Nature of toxemias of pregnancy, *Jr. Am. Med. Assoc.*, 1938, cx, 329.
8. LONGCOPE, W. T.: Chronic bilateral pyelonephritis: its origin and its association with hypertension, *ANN. INT. MED.*, 1937, xi, 149.
9. RYTAND, D. A.: Pathogenesis of arterial hypertension in coarctation of the aorta, *Proc. Soc. Exper. Biol. and Med.*, 1938, x, 11.
10. SCHROEDER, H. A., and STEELE, J. M.: Abnormalities of the urinary tract in "essential hypertension," *Proc. Soc. Exper. Biol. and Med.*, 1938, xxxix, 107.
11. HARRISON, T. R.: Failure of the circulation, 2nd Ed., 1939, The Williams and Wilkins Co., Baltimore, pp. 396.
12. PRINZMETAL, M., and OPPENHEIMER, E. T.: Rôle of arteries in peripheral resistance to hypertension, *Proc. Soc. Exper. Biol. and Med.*, 1937, xxxvi, 675.
13. BRAUN, L.: Experimentelle Untersuchungen über Blutdruck und Niere, *Wien. klin. Wchnschr.*, 1933, xlv, 225 and 1471; Also *ibid.*, 1934, xlvii, 65 and 131.
14. GOLDBLATT, H.: Studies on experimental hypertension; pathogenesis of experimental hypertension due to renal ischemia, *ANN. INT. MED.*, 1937, xi, 69.
15. BLALOCK, A., and LEVY, S. E.: Studies on etiology of renal hypertension, *Ann. Surg.*, 1937 cvi, 826.

V. CUTANEOUS XANTHOMATOSIS *

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THE purpose of this paper is to present a working classification of cutaneous xanthomas,^{1, 2, 3} with brief mention of their distinguishing features, and to report a case of extensive xanthoma tuberosum in which no evidence of systemic disease could be demonstrated despite a very marked increase in the blood and tissue lipoids.

TYPES OF CUTANEOUS XANTHOMATOSIS WITH DISTINGUISHING FEATURES

1. *Nevoxantho-endothelioma* (McDonagh):

Onset early in life. Groups of papules or nodules on extensor surfaces.

Spontaneous involution.

Normal blood lipoids.

Characteristic histopathologic picture, including endothelial, as well as Touton, giant cells.

2. *Juvenile xanthoma*:

Usually presents characteristics of type 3 (below), occasionally of type 4.

Rarely presents characteristics of a combination of types 3 and 4, with or without evidence of Hand-Schüller-Christian disease.

Hereditary tendency.

Frequent occurrence of severe cardiovascular disease, rarely of hepatosplenomegaly, with features of both types 3 and 4.

3. *Xanthoma tuberosum* (the most common type):⁵

Nodules, papules, or plaques predominating on extensor surfaces, including tendon sheaths.

Definite hyperlipemia.

Usually an increase in cholesterol in both blood and cutaneous lesions.

Frequent association of severe cardiovascular disease, especially angina pectoris and intermittent claudication.

Involution of lesions frequently follows low-fat diet.†

* Submitted for publication July 25, 1938.

† Thannhauser and Magendantz referred to xanthomatosis of the central nervous system described by van Bogaert and others in association with xanthoma of the tendons and xanthoma tuberosum. So-called extracellular cholesterosis of Urbach can also, I believe, be regarded as a variant of xanthoma tuberosum.^{1, 4}

4. *Xanthoma disseminatum*:

Fine papules and plaques predominating on flexural surfaces, especially axillary folds, and also mucous membranes, including pharynx and larynx.

Frequent involvement of pituitary region and associated mild diabetes insipidus.

Normal blood lipoids.

Tissue lipoids as in type 3.

No response to any diet or other type of treatment.

5. *Xanthelasma of eyelids*:

May be seen in any type of xanthoma, especially types 3 and 4.

Moderate elevation of blood lipoids occurs in 70 per cent of cases of xanthoma limited to eyelids alone.

Often associated with severe cardiovascular disease.

Histopathologic picture is typical for xanthoma.

6. *Xanthoma diabeticorum*:

Multiple discrete to confluent papules predominating on extensor surfaces with predilection for palms and soles.

Usually a severe diabetes with marked lipemia and prompt involution under diet and insulin.

Involuting lesions reveal extracellular as well as intracellular deposits of lipoids outlining the reticulo-endothelial system.

7. *Necrobiosis lipoidica diabeticorum*:

Varying sized plaques, chiefly on extremities; may follow trauma.

Usually associated with diabetes.

Normal blood lipoids.

Characteristic histopathologic picture with central necrosis and extracellular deposits of lipoids usually with an excess of free cholesterol in the tissues.

8. *Lipoid proteinose (Urbach)*:

Hereditary tendency.

Nodular, hyperkeratotic, verrucous and sclerosing lesions predominating on face, extremities, and mucous membranes, including larynx.

Histochemical evidence points to disturbance in phosphatides with extracellular deposits of lipoids about blood vessels.

9. *Xanthoma in relation to disease of the liver*:

Usually type 3, occasionally a combination of types 3 and 4, or type 4 alone in terminal stages.

Lesions on palms predominate.

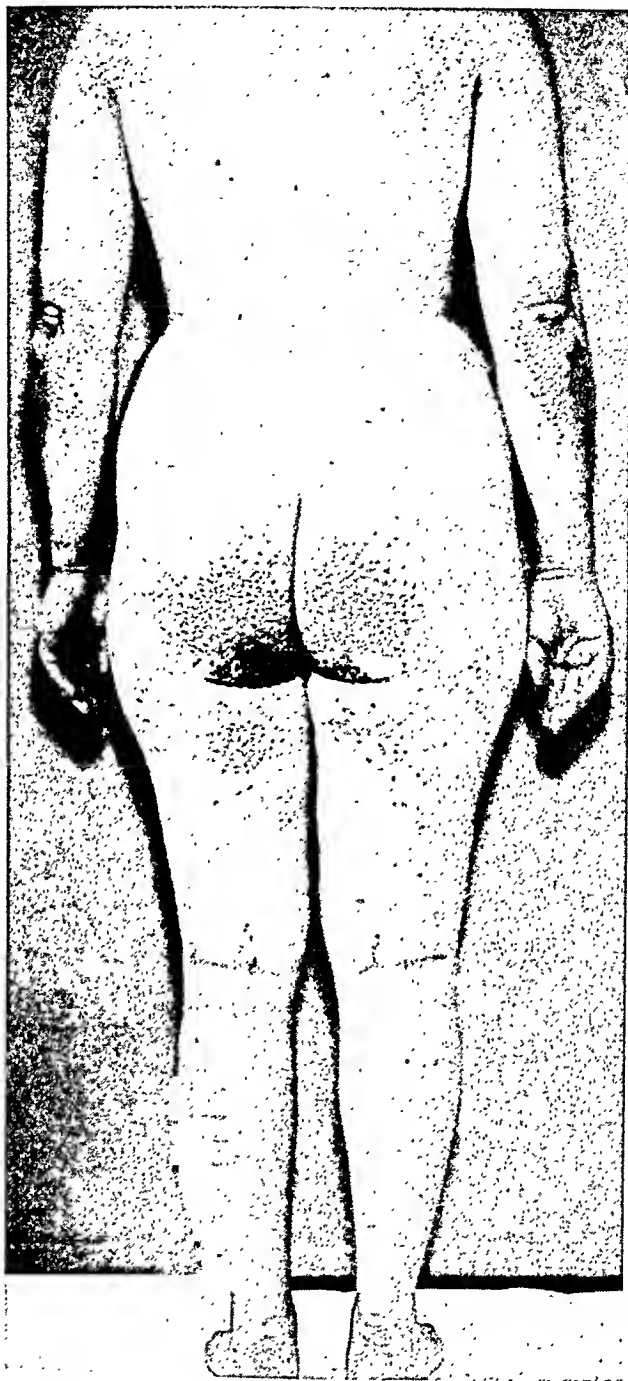


FIG. 1. Xanthoma tuberosum, involving extensor surfaces and also occurring in creases and folds of skin or in areas subject to friction.

Cutaneous xanthomas are usually secondary to hepatic involvement but may be primary. Hyperlipemia without relative increase in free cholesterol is the rule. Secondary xanthomatosis following obstructive jaundice associated with stricture of the common duct is the most common type;

also hepatosplenomegaly with cutaneous and mucous membrane lesions with or without jaundice and marked increase in phosphatides and free cholesterol in the blood and tissues.

10. *Xanthoma in relation to tumors:*

- a. So-called "xanthic tumors" of the tendon sheaths independent or associated with type 3. These are not malignant lesions. Hyperlipemia
- b. Histiocytoma (dermatofibroma). Usually a hyperlipemia.
- c. Xanthic changes in true malignant neoplasms. Distinguished by concomitant histopathologic findings.

CASE REPORT

A woman, aged 28 years, was examined at the Mayo Clinic in July, 1937, because of cutaneous lesions of six years' duration. These started as macular areas on both palms; nodules and papules then appeared on the extensor surfaces about the elbows, knees, Achilles tendon, heels, and hips. The lesions also appeared on the flexural

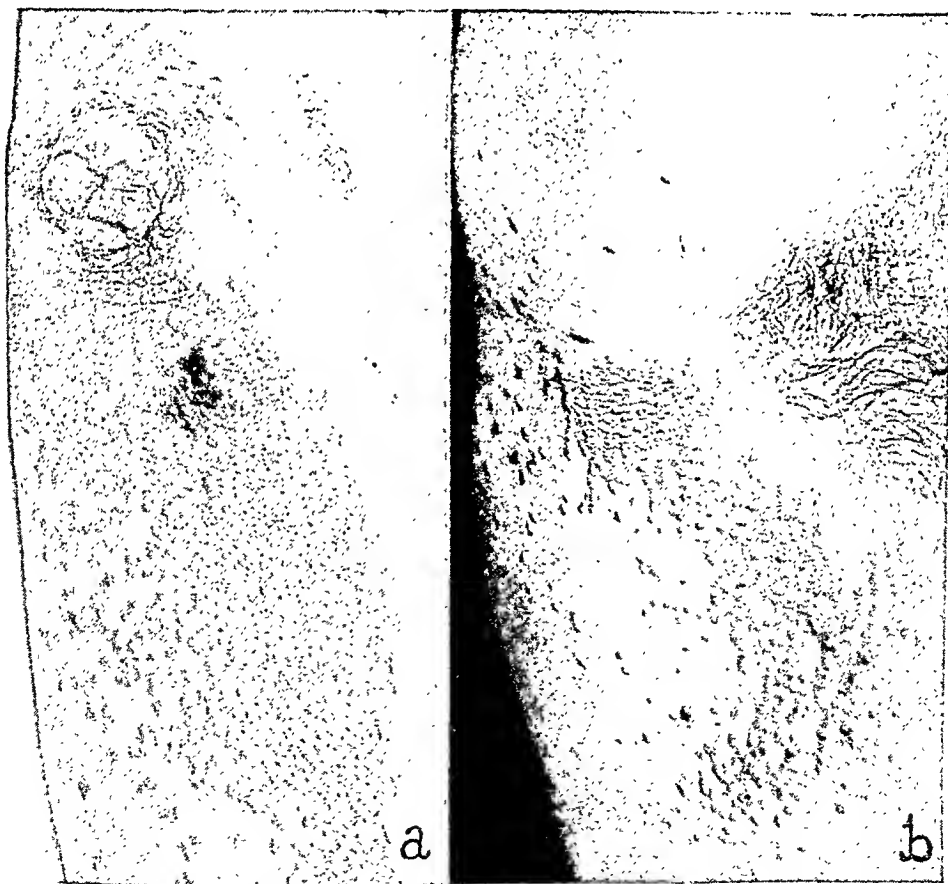


FIG. 2. Xanthoma tuberosum, showing *a*, xanthomas of various sizes and xanthomatous plaque on elbow, and *b*, xanthomas at margins of axilla. The deep axilla is not involved as is the case in xanthoma disseminatum.

surfaces of the elbows, axilla, wrists, and across the foot and groin. No history could be obtained of diabetes or diabetes insipidus, or of cardiorenal, hepatic, or other systemic disease. The family history was negative.

The nature of the lesions is shown in figures 1 and 2. It will be noted that where the lesions occurred on the flexural surfaces, they were in the creases or folds of the skin; elsewhere they occurred where there was friction from clothing. There was no involvement deep in the axilla. The lesions varied from a light yellow to reddish-brown; the older and larger lesions were of a deeper or brownish hue. General examination gave essentially negative results, including roentgenograms of the legs for occlusive arterial disease, and roentgenograms of the pituitary gland, sella turcica, and of the thorax. Electrocardiograms were essentially normal. There was no involvement of the mucous membranes of the mouth, larynx, or pharynx, or of the eyelids. The patient was somewhat obese, her height being 60 inches (152 cm.) and her weight 167 pounds (75.7 kg.). The liver could not be palpated. A liver function

TABLE I
Biochemical Studies of Blood and Tissue

Biochemical studies	Blood		Tissue	
	9-9-37		7-12-37	
	Mg. per 100 c.c. plasma	Per cent of total lipoids	Per cent of wet weight	Per cent of total lipoids
Total cholesterol	667	39	5.5	63
Cholesterol esters	417	62*	2.5	45*
Lecithin	594	34†	2.0	24†
Fatty acids	1056	61	3.27	37
Total lipoids	1723		8.7	

* Per cent of total cholesterol.

† As per cent of total lipoids.

test revealed no retention of dye. The blood and tissue lipoids are given in table 1. A specimen for biopsy from early and late lesions revealed a typical picture of xanthoma with, however, a considerable amount of fibrosis.**

COMMENT

The onset of the xanthoma in this case was too late in life to class it as being of the juvenile type. The variation in color and size of the individual lesions was well shown, and also the fact that solid plaques sometimes occur in the tuberoses as well as in the disseminate forms of xanthoma. The lack of involvement of the mucous membranes or deeper portions of the axilla, the predominance of lesions on the extensor rather than on the flexural surfaces, together with the marked lipemia, ruled out xanthoma disseminatum. The involvement of the palms suggested the possibility of a diabetes or

** After this paper was submitted, the patient returned to the Mayo Clinic in August, 1938. There had been no change in the cutaneous lesions and the value for blood lipoids was practically the same. The patient had failed to follow an animal-fat-free diet. There was still no evidence to be found of systemic involvement of any type.

hepatic disease, but this could not be demonstrated. The increase in free cholesterol, as contrasted with combined cholesterol, in the tissues is probably best explained on the basis that the lesion chosen for analysis was an old one, revealing histologically, a great deal of fibrosis and a great deal of extracellular deposits of lipoids. As a result of my own experience and on reviewing the literature it seems that when, histologically, many of the lipoids are to be found extracellularly, there is likely to be either an excess of free over combined cholesterol or an increase in lecithin.⁴

This case therefore illustrates that a disturbance in the cholesterol-cholesterol ester ratio does not necessarily imply hepatic disease. We must regard it as an atypical but extensive case of xanthoma tuberosum, uncomplicated at the present time by any demonstrable involvement of the internal organs. Classification of various types of cutaneous xanthoma is important from the standpoint of prognosis and treatment, and also in regard to the type and location of the systemic involvement.

REFERENCES

1. MONTGOMERY, HAMILTON, and OSTERBERG, A. E.: Xanthomatosis: correlation of clinical, histopathologic, and chemical studies of cutaneous xanthomas, *Arch. Dermat. and Syph.*, 1938, xxxvii, 373-402.
2. MONTGOMERY, HAMILTON: Xanthomatosis; a systemic disease, *Proc. Staff Meet. Mayo Clinic*, 1937, xii, 641-644.
3. MONTGOMERY, HAMILTON: Xanthomatosis: III. Cutaneous xanthoma, especially in relation to disease of the liver, *Jr. Invest. Dermat.*, 1938, i, 325-351.
4. MONTGOMERY, HAMILTON, and HAVENS, F. Z.: Lipoid proteinosis (phosphatide lipoidosis), *Arch. Otolaryng.*, 1939, xxix, 650-666.
5. THANNHAUSER, S. J., and MAGENDANTZ, H.: Different clinical groups of xanthomatous diseases; clinical physiological study of 22 cases, *Ann. Int. Med.*, 1938, xi, 1662-1746.

THE MECHANISM OF THE PSYCHONEUROSES *

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IN the more recent classifications of the psychoneuroses there is a marked trend towards simplification. An attempt is made to class the psychoneuroses as prepsychotic anxiety states. While we are frequently forced to recognize this in our statistical records, there are many cases in which the clinical syndrome does not justify such a classification. The classification which is considered in this discussion is that adopted by the Committee on Statistics of the American Psychiatric Association, and the National Committee for Mental Hygiene in 1934. Accordingly, under this heading are placed disorders of psychogenic origin, or without clearly defined tangible cause or structural change.

PSYCHONEUROSES

1. Hysteria (anxiety hysteria, conversion hysteria).
2. Psychasthenia, or compulsive states.
3. Neurasthenia.
4. Hypochondriasis.
5. Reactive depression.
6. Anxiety states.
7. Mixed psychoneurosis.

The conception of anxiety hysteria¹ is extremely variable. According to one viewpoint, anxiety hysteria is conversion hysteria accompanied by anxiety. Another method of classification includes under anxiety hysteria those reactions which are presented under the head of psychasthenia.² From still another viewpoint anxiety hysteria should be classified with the anxiety states.

Patients who present conversion symptoms or phobias, but who are relatively free from recurring attacks of anxiety are usually grouped under conversion hysteria or psychasthenia, although the cases showing predominantly obsessions, compulsive tics and spasms and phobias are preferably classified as psychasthenia. Because of the frequent combination of psychoneurotic symptoms in individual cases the classification of mixed psychoneurosis may be proper in many instances.

It appears therefore that hysteria is not a desirable designation, and is not an entity. The same is true of psychasthenia or compulsive states² and hypochondriasis,⁴ the latter occurring not infrequently in the major psychoses. A statistical record shows that 65 per cent of the cases diagnosed

* Received for publication February 25, 1938.

hysteria during a period of 10 years were later hospitalized, and classified as schizophrenia.

A very different type of disturbance, and with a more constant clinical picture, is neurasthenia,³ and while neurasthenia is regarded as an entity without an organic basis, there is undoubtedly a physiological dysfunction as the basic cause. The motor and mental fatigability, diminished power of concentration, low blood pressure and other inefficiencies are not without cause. This clinical picture is a marked contrast to the conditions previously described.

The reactive depressions,⁵ which show depression in reaction to obvious external causes that might naturally produce sadness, such as bereavement, sickness and financial and other worries, are in proportion to cause and effect when we consider the constitutional instability of the individuals so afflicted.

The anxiety states,⁶ presenting more or less continuous anxiety and apprehensive expectation, with paroxysmal exacerbations, associated with physiological signs of fear, precordial distress, palpitation, dyspnea, nausea, gastrointestinal distress, diarrhea, emotional tension, irritability and intense self-preoccupation, present physical manifestations sufficient to be regarded as causative factors.

Such is the psychopathological aspect of the psychoneuroses.

However, whether or not our present understanding of the psychoneuroses qualifies us to speak of them as pathological units, our working hypothesis will be more fruitful if we postulate that there are such units, provided that we realize our classification is a mere scaffolding, to be discarded without emotion or egoism when a more solid structure appears. Our understanding of certain of the psychneuroses has reached the point where etiology, clinical syndrome, diagnostic criteria and pathology are recognizable.

The regularity with which certain psychneuroses occur in the same body types and the regularity with which other physical signs appear, strengthen the theory that the entire range of mental disorders, including the psychoneuroses, has a somatic basis intimately related to glandular balance, and since there are constitutional types conveniently summarized in the physique, so also are there temperamental types for which the word *psychique* is available.

The asthenic or asthenic-athletic physique is more often of the schizophrenic reaction *psychique*, as in hysteria, psychasthenia and hypochondriasis, while the pyknic habitus and the cycloid temperament are the rule as in neurasthenia, reactive depression and anxiety states. Furthermore, there are more or less constant physical manifestations intimately associated with the asthenic and asthenic-athletic physique and the schizoid *psychique* which differ materially from those observed in the pyknic habitus and the cycloid temperament.

It was possible to classify 400 cases of psychoneuroses into the following two groups on a somatic basis:

Hysteria A. Psychasthenia Hypochondriasis	{ Asthenic and asthenic-athletic habitus. Spasm of the radial arteries. Acrocyanosis. Dermographia. Segmental hypothermia. Excessive sweating and saliva.
Neurasthenia B. Reaction depression Anxiety states	{ Pyknic habitus. Small pulse volume, low blood pressure. Pale skin. Segmental hyperthermia. Anorexia, gastrointestinal and genitourinary disorders.

It is in group B that we frequently find gastrointestinal disturbance, changes in tonus of the stomach and bowel, in the secretions, and change in the tonus of the genitourinary apparatus, while in group A disturbances of the peripheral circulation are more common; vessel spasm, cyanosis, etc. I fully realize that the emotions play an important part in the circulatory disturbance; on the other hand endocrine imbalance is an important factor in depressions, exaltations, fear and anger.

The dermatologist recognizes the influence of increased excitability and emotionality in certain skin conditions, and speaks of dermothalassia in compulsion neuroses, and of emotional urticaria, hysterical pemphigus, abnormal hair growth, anomalies of sweat and of the nails.¹

In these physical manifestations we recognize a disturbed mechanism of the human organism, intimately connected with the vegetative nervous system, and with a reciprocal relationship with the glands of internal secretion.

Associated with the physical manifestations there is a more or less constant psychic syndrome characteristic of each group. In group A the most constant mental characteristics are: Lack of attention, depression of spirits, loss of self-control, excitement without apparent cause, uncontrollable emotional outbursts, laughing or weeping, insidious loss of power of decision, and unwillingness to assume responsibility.

In group B the most apparent and constant psychic syndrome is that of sadness, fear, anxiety and hopelessness, with mild agitation, intense self-preoccupation, and inadequacy.

We realize therefore, that there can be disturbance of the function of the central nervous system as the result of abnormal working of either the endocrine mechanism or of the parasympathetic and sympathetic nervous systems; just as there might be impaired activity of the glands of internal

secretion or of the vegetative nerves secondary to deranged function of the central nervous system. We also recognize that the manifestations in the psychoneuroses may be the result of abnormal function of other bodily organs, and of general toxic or infectious processes which indirectly affect the nervous system. A peripheral vasospasm may also mean a cerebral vasospasm, while a secondary anoxemia, or a toxic state, bacterial or chemical, may bring the same result.

If we apply the theory that a balance exists between the activities of the sympathetic and the parasympathetic division so that visceral function is resultant of the balance of these two forces, and translate the anatomic units of this conception into chemical terms, the activity of any organ involved by autonomic stimulation is the result of a balanced activity between acetylcholine, which is produced by the *parasympathetic nervous system*, and the more hypothetic series of chemical substances produced by the *sympathetic nervous system* at the neurovisceral junction, which are called sympathin E. and I. These are like adrenin, so the chemical concept of balance may be stated as the result of the effects of cholinergic and adrenergic substances. To this concept has been added the hypothesis of the activity of the esterases, substances produced either by the reacting cell or by the tissues in general. These substances (choline-esterase) are believed to destroy acetylcholine, and consequently the action of the parasympathetic nervous system is intermittent. The antagonist which acts on sympathin in a similar manner has not been isolated.

Experimental evidence shows that while some functions of an organ are apparently autonomically balanced, there are other functions in the same organs which respond to only one type of drug, and consequently are either cholinergic or adrenergic. The sweat glands are cholinergic; they respond only to chemicals of the acetylcholine group and not at all to the chemicals of the adrenergic type, although they are innervated only by the sympathetic system, and would be expected to react to adrenergic chemicals.²

According to this theory the normal activities of the sympathetic and the parasympathetic division of the autonomic nervous system are dependent upon a balance between two forces. A disturbance of this equilibrium will interrupt the normal activity of any organ involved by autonomic stimulation, resulting in physical manifestations which may be perceived subjectively or objectively.

The results of research which began in 1928 gave us a more tenable concept of many of the physical and also of some of the mental manifestations of the psychoneuroses.

The cases were selected according to body types, physical signs and mental manifestations, as indicated in groups A and B, and 200 cases of each group were treated. The patients in group A were below the age of 30 years, and those in group B under 35 years. The youngest patient was 12 years old.

1. The experimental results with a mixture of CO_2 (20 per cent), and O_2 (80 per cent) in group A were rather striking, and all out of proportion to what one might expect with psychotherapy alone. I am fully aware that this type of treatment may be regarded as psychotherapy, but the patients were immediately relieved of the physical as well as of the mental manifestations. They expressed a feeling of well-being. The objective physical reaction occurred in the following order: General flushing and warming of the skin, muscular hypertonus, relaxation of all muscles and moisture of the skin. However, this treatment does not bring permanent relief, and within 24 hours all of the physical and mental signs recur. Repeated applications give the same results.

The mechanism of the action of CO_2 and O_2 is that the CO_2 is a vasodilator and cholinergic in function, while O_2 increases the blood flow to the brain. This has been definitely proved by animal experiments.³ This reaction results in a fixation of oxygen by the cell dependent upon the acquisition of free oxygen from without.

The application of this experiment in types listed under B gave unsatisfactory results. No change in the physical signs or mental manifestations was noted after the treatment.

2. A much more permanent result was obtained by oral administration of hyoscin hydrobromide ($\text{C}_{17}\text{H}_{21}\text{O}_4\text{NHBR}$) over a longer period of time. To avoid any physiological disturbance such as dryness of the mouth and throat, dilation of the pupils, etc., the drug was given in small doses, gradually increased from 1/300 grain to 1/75 grain. The dose is increased at intervals of eight days until the maximum dose is reached. In this manner all patients acquired a tolerance without any physiological disturbance.

The physical signs and mental manifestations gradually disappeared giving a more or less permanent result. Hyoscin hydrobromide is a vasodilator, slows the pulse rate, raises the pulse volume and increases the blood flow to the brain.

The application of this drug in group B was unsatisfactory.

It appears, therefore, that $\text{CO}_2\text{--O}_2$ and hyoscin hydrobromide are cholinergic in function.

3. Benzedrine sulfate (benzyl-methyl carbamine) was used as an adrenergic drug in both groups with unsatisfactory results with group A. Much more gratifying were the results with group B, especially in those cases where mental depression was a prominent sign, and gastrointestinal and genitourinary hypertonus existed.

Benzedrine sulfate increases the blood pressure and relaxed spasm of the gastrointestinal tract and relieves bladder hypertonus of the functional or organic type.

Ephedrine and epinephrine are adrenergic drugs. The results with these drugs were not definite in group A. Ephedrine was the most satisfactory in group B. Many cases found in group B were decidedly benefited

by digifolin (representing digitalin and digitoxin). Coramine (pyridine-B carboxylic acid diethylamide) gave good results in relieving the mental depression in the reaction depressions and the anxiety states.

In many of these cases with low blood pressure, small pulse volume, pale skin, the mental manifestations are apparently dependent upon a cerebral anoxemia. Since the arterial blood supply is dependent upon systemic pressure, any of the factors known to reduce arterial pressure, such as reduced systolic discharge, the result of myocardial inefficiency, decreased conductivity of the bundle of His, lowered peripheral resistance and decreased heart rate reduce venous return, diminishing the cerebral blood flow to a degree lower than is necessary to maintain cerebral function with a consequent anoxemia, and since the adrenergic drugs and those drugs which increase the myocardial force are beneficial, it would appear that a cerebral anoxemia exists.

The case histories related below are representative of patients selected for this work. Only positive findings are recorded.

CASE REPORTS

Case 1. White male, aged 19, asthenic body type. Complained of numbness of the legs, coldness of the hands and feet, anxiety attacks with palpitation of the heart, and shortness of breath. Lacks ambition, and has difficulty in applying himself. This condition came on at the age of 14, and has been more or less continuous.

He has had no other serious illness, and no injury. Tonsillectomy and adenoidectomy were performed at the age of 10 years.

The patient is the second child of a family of four, and has two brothers and one sister, all well and normally active. The father is 50 years old, emotionally stable, and a man of good habits. The mother is of nervous temperament, aged 43.

The examination revealed asthenic habitus, weight 149 pounds, height 72½ inches. Spasm of the radial arteries, acrocyanosis, pulse 84. B.P. 140 mm. of mercury systolic and 80 diastolic. Cold hands and feet, wet palms and soles. Mild anxiety, over-apprehensiveness and a feeling of insecurity.

Hyoscin hydrobromide was administered orally according to the method described above. In five weeks the patient was entirely free from the symptoms described.

Case 2. A white female, aged 16. Asthenic habitus. Complained of attacks in which she feels like falling. This occurs sometimes when she is sitting down or standing erect. Sometimes she awakens in the night calling out that she is falling. She has no recollection of this the following morning. She also has frontal headache and pain in the eyes. She stated that she is easily frightened. The first attack came on at the age of 14 years. Since then the attacks have been recurring at two or three day intervals.

She has had no serious illness. Fracture of the wrist and injury to the knee occurred from a fall; good recovery. Tonsillectomy at 11 years.

The patient lives on a farm, attends the community school, and is in the ninth grade. Her scholastic record is good.

The father is 50 years of age. He is irritable and nervous. The mother is well, even-tempered and cheerful. There are four brothers, all well, and two sisters, both well.

The examination showed a well nourished young girl without physical deviations, weighing 110 pounds; 5 feet 5 inches in height. B.P. 120 systolic and 70 diastolic.

Spasm of the radial arteries. Pulse 64 per minute. The hands and feet are cyanosed. Palms and soles wet; marked dermatographia. She was in a cheerful mood, with good contact and normal behavior.

Histamine was given orally for a four week period, with temporary relief. Hyoscin hydrobromide relieved her condition.

Case 3. White male, aged 32, pyknic habitus. Became mildly depressed and withdrew from all social activities. He feared that he had cancer of the gastrointestinal tract. He complained of general weakness, gastrointestinal distress, gaseous distention of the abdomen, eructations, alternating constipation and diarrhea, and enuresis. He was no longer able to apply himself to his occupation as an attorney at law. This difficulty was of about 10 years' standing. Prior to the present illness the patient was in good health, and since his childhood days has had no serious illness or injury.

His childhood days were happy and he has always been fond of out-of-door activities. He graduated from a University law school and practiced law until three years ago. He is single, and has no unusual responsibilities.

The father died of cancer of the duodenum at 62, and one paternal uncle and one aunt died of cancer. Mother is well at 70.

The physical examination revealed moderate distention of the abdomen, spastic radial arteries, cold hands and feet, palms and soles wet. He was extremely over-apprehensive, fearful, restless, and emotionally unstable.

Benzedrine sulfate was administered orally in 10 mg. doses twice daily, which gave him relief from the gastrointestinal distress and the enuresis. He regained his confidence and was able to return to his former occupation within five weeks.

Case 4. A white female, aged 28, pyknic body type, was subject to recurring attacks of mild mental depression, emotional instability and a feeling of inadequacy. She had been obliged to discontinue her occupation as a teacher on several occasions for from three months to a year. These attacks came on when she was 18 years of age. Prior to this time her health was good and she has had no serious illness.

The father and mother were separated and her home life was unhappy. She is single and is active socially.

The physical examination revealed a small pulse volume. B.P. 100 systolic and 65 diastolic. Heart sounds weak and not easily heard; no murmurs, thrills or irregularity. Her general muscular tone was diminished, the grip in both hands was weak.

Adrenal cortex, in increasing doses to tolerance, raised the pulse volume, the blood pressure, relieved the mental depression, and the patient was able to return to her occupation within six weeks.

Case 5. A white female, aged 32, pyknic body type, complained of gastrointestinal distress, irritable bladder, emotional instability, irritability and mental depression. This difficulty was of five years' standing, and the patient had been repeatedly told by physicians that she had a spastic colitis, and she became fearful that she had a serious organic illness from which she would not recover.

Prior to the present illness the patient's general health was good. She had a tonsillectomy at the age of 13, and an appendectomy at 21, with good recovery. The menstrual history is negative.

Her childhood was happy. She has always been active, and normally of cheerful disposition until she became ill, when a marked change in personality was noted. She was married at 30, and was happy in her family life. Before her marriage she was a teacher. Her father died of uremia at 80. Mother is living and well at 82. One sister died after an illness of eight years, cause not known.

The patient is well developed. Skin pale, muscles well developed, muscle tone diminished. Pulse, small volume, regular, 64 per minute. B.P. 96 systolic and 70 diastolic. Otherwise the physical and neurological examinations were negative.

The patient was talkative, she stressed the topic of colitis and the suffering caused by it. She was in a depressed mood, had frequent crying spells, and a hopeless outlook. She was well oriented and her memory was good. Her attention was variable. Her replies to questions were prompt, coherent and relevant.

Digifoline was given orally in increasing doses, from 10-15 minims three times daily. The patient made a good recovery.

SUMMARY

1. Four hundred cases were selected for this study.
2. It was possible to group 200 cases of hysteria, psychasthenia and hypochondriases according to body type, physical signs and mental manifestations, under one head (A), and 200 cases of neurasthenia, reaction depression and anxiety states, on the same basis, under another head (B).
3. There is a close relationship between the asthenic and asthenic-athletic habitus and hysteria, psychasthenia and hypochondriasis; and between the pyknic habitus and neurasthenia, reaction depression and the anxiety states.
4. The reaction to drugs is antagonistic between the two groups. The conditions grouped under A react favorably to cholinergic drugs, while those in group B are antagonistic to cholinergic drugs but react favorably to adrenergic drugs.
5. Carbon dioxide and oxygen inhalations give relief of the physical and mental manifestations in group A, but give no relief in group B.
6. There is a peripheral vasospasm and increased vascular tension in the psychoneuroses of group A, and diminished peripheral vascular tension in those of group B. If there is also a cerebral arteriolar spasm the result would be a deficient degree of oxygenation and a reduction in the volume of blood referred to the brain or the nervous system as a whole. The same would be true of group B, the result of a peripheral hypotension. The physical and mental manifestations and the drug reactions are in harmony with this view.

REFERENCES

1. ELLER, J. J.: Neurogenic and psychogenic disorders, *Med. Jr. and Rec.*, 1929, cxxix, 554.
2. MYERSON, ABRAHAM: Human autonomic pharmacology. XII. Theories and results of autonomic drug administration, *Jr. Am. Med. Assoc.*, 1938, cx, 101.
3. SCHMIDT, CARL F.: Unpublished data.

THE PLASMA LIPOIDS IN ARTERIOSCLEROSIS OBLITERANS *

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THE pathogenesis of arteriosclerosis has been the subject of controversy for many years. Among certain investigators there has arisen the concept that the development of atheroma is associated with disturbances of lipid metabolism. The chief reasons for this can be summarized as follows: Pathologists from the time of Virchow⁶ have noted the presence of comparatively large amounts of both cholesterol and neutral fat in atheromatous formations even in their earliest stages of development. More recently Leary^{11, 12} has concluded that the development of the entire picture of arteriosclerosis is associated with these lipid deposits and subsequent reaction of the vascular tissue to them. Atherosclerotic lesions can be produced in rabbits by the dietary administration of animal fat or cholesterol, rabbits in these cases developing lipemia and hypercholesterolemia because of their inability to metabolize the animal lipoids satisfactorily. This was first described in 1908, by Ignatowski,⁹ who fed rabbits milk and eggs, and later in 1913 by Anitschkow and Chalutow,¹ who fed them cholesterol. It has been confirmed by Wacker and Hueck,¹⁰ Bailey,² and Leary.¹³ Huber and his co-workers⁸ found that administration of lipocaic to rabbits that were given animal fat prevented the development of the atheroma. Atherosclerosis is commonly seen in association with lipemia in man. In a series of 27 patients who had marked lipemia and hypercholesterolemia associated with xanthoma tuberosum of the skin, Montgomery and Osterberg¹⁵ found a high percentage of coronary sclerosis and arteriosclerosis obliterans of the legs (37 per cent). Necropsy examination in a case of marked lipemia reported by Ochsner and Connor¹⁶ showed an extreme degree of diffuse atherosclerosis. It has been stated by Leary that the incidence of extensive and premature atherosclerosis in diabetic patients was much higher during the period when these patients were fed diets containing large amounts of fat as part of their treatment. This point, however, is somewhat controversial.

Reports concerning the levels of blood lipoids in patients with atherosclerosis in various parts of the body have not been consistent. Mjassnikow¹⁴ found the blood cholesterol usually increased in aortic arteriosclerosis but not increased in a few cases of peripheral arteriosclerosis. Landé and Sperry¹⁰ determined the cholesterol content of serum obtained at necropsy in patients dying accidental deaths who had extensive aortic atherosclerosis and found it no higher than in patients without these lesions. Davis, Stern and Lesnick⁷ found the average free and total cholesterol,

* Read at the New Orleans meeting of the American College of Physicians March 28, 1939.

lipid phosphorus and fatty acids of the blood higher in a group of patients with angina pectoris than in a group of control subjects, although there was considerable overlapping of individual values in the two groups.

Some confusion exists in the literature as to the use of the terms arteriosclerosis and atherosclerosis. Some pathologists have attempted to make a distinction between arteriosclerosis, a degenerative disease of the medial coat of the artery, and atherosclerosis, a disease where the essential change is the development of subendothelial atheroma. A clean-cut differentiation is usually not possible, since the two conditions are usually co-existent. However, their relative proportions may vary greatly.

From the pathologic standpoint arteriosclerosis obliterans of the legs does not differ from occlusive arteriosclerosis or atherosclerosis elsewhere in the body. The lesion consists of three essential components: (1) Degeneration of the medial coat; (2) extensive formation of atheroma, and (3) thrombosis. In the majority of cases the most important component appears to be the atheroma because this forms a considerable portion of the occluding mass and because degeneration of its intimal surface is the main factor in the formation of the thrombus which finally occludes the lumen. In advanced cases the lesions are usually extensive and often associated with considerable atherosclerosis of the abdominal aorta.

This study is based on the determinations of the plasma lipoids in 73 cases of arteriosclerosis obliterans of the legs. These patients did not have diabetes mellitus, as evidenced by normal blood sugar determinations and the absence of glycosuria. Also, they did not have evidence of hyperthyroidism or hypothyroidism. The criteria for making the diagnosis of arteriosclerosis obliterans consisted in definite evidence of occlusion of the major arteries (femoral, popliteal and posterior tibial) of one or both legs, with evidence of arterial insufficiency of the leg muscles or feet, the presence of roentgenographically visible calcification of the arterial walls, the onset of symptoms after the age of 40 years in all cases and after the age of 50 years in 63 of the 73 cases and the absence of a history or findings of superficial thrombophlebitis. In a number of the cases the nature of the lesion was confirmed by pathologic study. The ages of the patients varied from 40 to 79 years.

For comparison the plasma lipoids were studied in a series of 200 individuals of various ages who were considered normal. The criteria for considering these patients normal consisted in the absence of evidence of cardiac or vascular disease, metabolic disorders, diabetes mellitus or dermatoses, as well as the absence of physical findings of any organic disorder.

In both groups determinations were made of the total plasma lipoids and the four fractions, cholesterol, cholesterol esters, phospholipids and fatty acids. The Bloor method^{3, 4, 5} was used for determining the total lipoids and all fractions except the phospholipids, which were determined by the method of Youngburg and Youngburg.²⁰ The blood for the determinations was withdrawn in the morning with the patients fasting. Repeated

determinations on certain of the individuals on different days showed only very small variations in values for the various lipoids from day to day, as has been noted by other investigators.

TABLE I

Concentration of Lipoid Fractions and Total Lipoids in the Plasma of Normal Persons and of Persons Suffering from Arteriosclerosis Obliterans

Control series							
Age	No. cases		Mg. cholesterol per 100 c.c. plasma	Mg. cholesterol esters per 100 c.c. plasma	Mg. phospholipids per 100 c.c. plasma	Mg. fatty acids per 100 c.c. plasma	Mg. total lipoids per 100 c.c. plasma
10-19	3	Mean Range	160 146-187	114 93-137	194 187-208	307 264-330	467 441-517
20-29	66	Mean Range	203 141-309	143 89-241	205 167-278	323 229-484	526 365-753
30-39	53	Mean Range	215 135-292	149 91-214	219 166-278	343 221-492	556 375-769
40-49	41	Mean Range	232 167-370	167 111-309	234 159-316	384 287-651	616 470-919
50-59	25	Mean Range	244 175-354	174 120-268	235 185-309	384 253-579	628 461-827
60-69	11	Mean Range	233 192-303	163 99-214	240 212-315	357 286-492	590 478-784
70-79	1	Mean	172	123	253	393	565
Total	200	Mean Range	218 135-370	154 89-309	220 159-316	350 221-651	568 365-919
Arteriosclerosis obliterans							
40-49	8	Mean Range	290 245-333	208 181-232	266 176-450	454 332-550	744 550-868
50-59	28	Mean Range	275 172-378	194 124-321	284 207-372	431 232-734	706 551-1061
60-69	23	Mean Range	269 214-347	190 152-225	278 203-378	396 249-593	665 487-902
70-89	14	Mean Range	215 139-327	160 88-261	222 120-321	372 225-646	587 404-973
Total	73	Mean Range	263 139-378	186 88-321	267 120-450	411 225-734	674 404-1061

A summary of the results in both groups is given in table 1, which shows mean and range for the various lipid fractions in each group and in the various age decades of both the series of cases of arteriosclerosis

obliterans and the control series. It should be noted that the age distribution in the two series is not exactly parallel. However, a fairly large series of cases in both the control and the arteriosclerotic groups falls between the ages of 40 and 69 years.

It is noteworthy that the range of values for total lipoids and for each fraction is rather great in the control group. This has been noted by other investigators. It is also noteworthy that there is an increase in the mean values in each succeeding decade up to the age of 60 years, after which there is a slight decline. It might be argued that in selecting a group of normal persons for comparison with arteriosclerotic patients only young individuals should be used, as even after the age of 30 years many might have undetectable although well-developed arteriosclerosis of the aorta or other visceral arteries. Equally good arguments can be advanced for comparing only corresponding age groups. However, this point is of more theoretic than practical importance, since either method of selecting the controls leads to essentially the same conclusion.

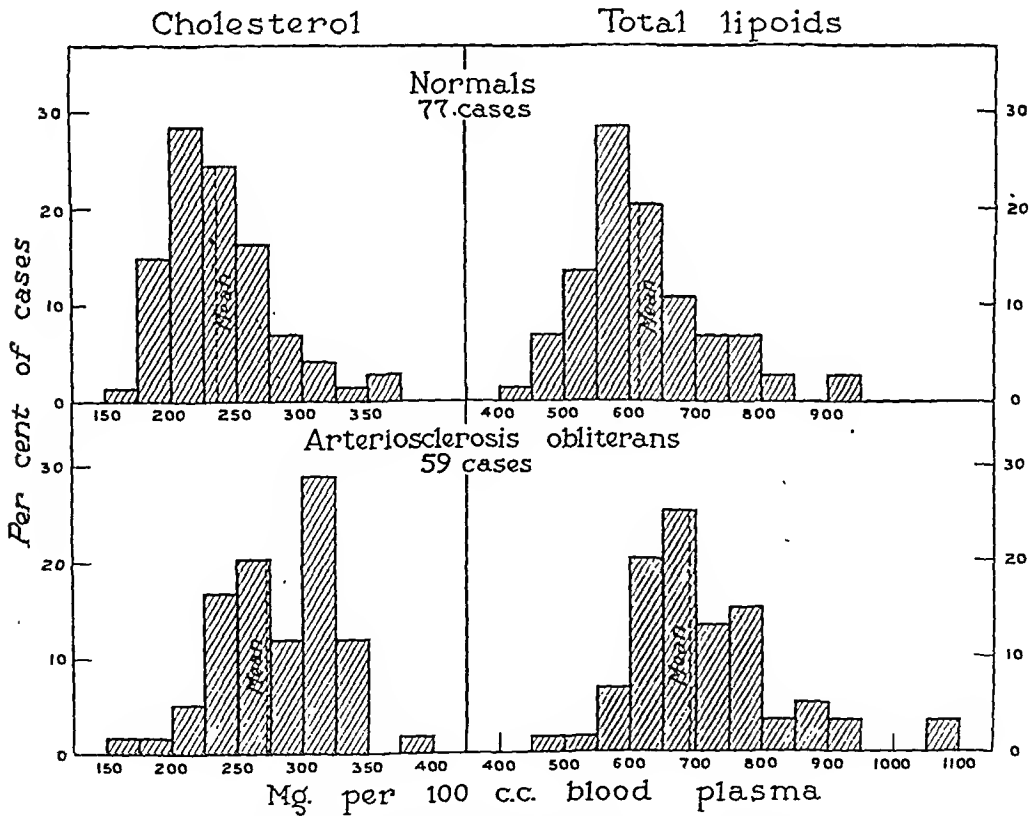


FIG. 1. Frequency distribution of plasma cholesterol and total lipoids in the control series and in patients with arteriosclerosis obliterans in the same age groups (40-69 years).

A comparison of the control cases and the cases of arteriosclerosis obliterans with regard to range of the total lipoids and various fractions shows very little difference between the two. However, there is a definite differ-

ence in the means, these being consistently greater in the arteriosclerotic group. The same is apparent if one compares only those cases in each group which fall within certain age decades (40-49, 50-59 and 60-69), although the difference is slightly less than it is in a comparison of the entire groups. The difference in mean values is essentially proportional for each of the lipid fractions.

Figure 1 shows the frequency distribution of the plasma cholesterol and total lipoids in the control series and patients with arteriosclerosis obliterans between the ages of 40 and 69 years. There is a considerably larger percentage of higher values in the arteriosclerotic group, particularly of cholesterol higher than 300 mg. per 100 c.c. and total lipoids higher than 700 mg.

In considering the plasma lipid values in the group of arteriosclerotic patients alone it is noteworthy that there is in general a gradual decrease in mean values for each fraction with increasing age and that in the 14 patients between the ages of 70 and 89 years the mean values were approximately the same as the means for the entire normal group (table 1). One possible reason for this is that most of these elderly patients had gangrene, had eaten poorly and had lost weight as the result of persistent pain, loss of sleep and chronic toxemia.

TABLE II

Concentration of Cholesterol and Total Lipoids in the Plasma of Normal Persons, of Persons Suffering from Thrombo-Angiitis Obliterans and of Persons Suffering from Arteriosclerosis Obliterans

		Mg. cholesterol per 100 c.c. plasma	Mg. total lipoids per 100 c.c. plasma
Control group 200 cases	Mean Range	218 135-370	568 365-919
Thrombo-angiitis obliterans (Roth, Maclay and Allen) 36 cases	Mean Range	192 102-273	563 360-871
Arteriosclerosis obliterans 73 cases	Mean Range	263 139-378	674 404-1061

Another comparison is made in table 2, in which mean and range values for plasma cholesterol and total lipoids in the arteriosclerotic and control groups are compared with similar values obtained in a study of patients with thrombo-angiitis obliterans by Roth, Maclay and Allen.¹⁷ The determinations of the blood lipoids in the cases of thrombo-angiitis were done under the same conditions, by the same technicians and in the same laboratory as for the control and arteriosclerotic groups. It will be noted that the mean values in this series of cases of thrombo-angiitis obliterans are actually lower than in the control series and that in none of the cases of thrombo-angiitis did the cholesterol exceed 273 mg. per 100 c.c. of plasma. It seems justified to state, therefore, that in a patient with chronic occlusive arterial

disease of the lower extremities where the exact nature of the lesion is indeterminate by other criteria a plasma cholesterol value of more than 300 mg. per 100 c.c. is definitely supportive evidence for a diagnosis of arteriosclerosis obliterans, and that a plasma lipid value of less than 200 mg. per 100 c.c. is definite, although not certain, evidence in favor of the diagnosis of thrombo-angiitis obliterans.

In a recent publication by Turner and Steiner¹⁸ it was stated that in normal individuals it is not possible to reduce the concentration of the cholesterol in the blood by diet. Eight of the 73 patients with arteriosclerosis obliterans included in this study were given a low fat diet. This consisted of carbohydrate 420 gm., protein 60 gm., and fat 30 gm., of which 15 gm. were animal fat; the diet was supplemented by one capsule of haliver oil a day. This diet was well tolerated by all the patients. In four of the eight no reduction in the plasma lipoids occurred. In the other four definite reduction occurred (table 3). In case 3 pulsations in the

TABLE III
Effect of Low Fat Diet in Arteriosclerosis Obliterans

		Mg. cholesterol per 100 c.c. plasma	Mg. phospho- lipids per 100 c.c. plasma	Mg. total lipoids per 100 c.c. plasma
Case 1	Before diet	287	255	739
	After diet 2 mos.	241	232	572
Case 2	Before diet	321	348	735
	After diet 2 wks.	245	316	635
Case 3	Before diet	260	243	656
	After diet 4 wks.	198	232	570
Case 4	Before diet	252	325	628
	After diet 2 wks.	231	293	548

popliteal, posterior tibial and dorsalis pedis arteries, which had been absent, were found to be of almost normal volume after the patient had been on the diet for a year. Intermittent claudication disappeared coincidentally. It is possible that this was due to increased collateral circulation rather than to involution of atheroma.

During the period that this study of plasma lipoids in arteriosclerosis obliterans was being conducted, three patients were studied who had chronic occlusive disease of the arteries of their legs with slight calcification of the arteries in the roentgenograms, intermittent claudication, tuberous xanthomas of the skin and marked lipemia without diabetes mellitus. Because of the xanthomas and the very high plasma lipoids they were not included in the group of 73 cases mentioned in table 1. These patients were all

between 45 and 50 years of age. They were all given the low fat diet mentioned in the preceding paragraph and marked reduction of the plasma lipoids occurred (table 4), although patient 2 tolerated the diet rather

TABLE IV

Effect of Low Fat Diet in Arteriosclerosis Obliterans Associated with Xanthoma Tuberosum and Marked Lipemia

		Mg. cholesterol per 100 c.c. plasma	Mg. total lipoids per 100 c.c. plasma
Case 1	Before diet	667	2221
	After diet 1½ years	309	1131
Case 2	Before diet	657	1675
	After diet 5 mos.	333	1120
Case 3	Before diet	362	1604
	After diet 4 wks.	222	806

poorly and subsequently the plasma lipoids rose to levels greater than were originally obtained. Patient 1 was completely relieved of intermittent claudication and pulsations returned in the arteries of the legs after he had been on the diet one year.

In seeking an explanation for the evidence that plasma lipoids in cases of arteriosclerosis obliterans of the legs are usually but not consistently higher than normal mean values one can hypothesize that there may be two types of lesions, one seen usually in patients of middle age, in which the plasma lipoids are usually high, and one usually seen in older individuals, in which there is more evidence of degeneration of the medial coat and in which the plasma lipoids are normal or low. Another possibility to consider is that mild degrees of hyperlipemia may accelerate the development of atheroma or cause it to develop at an earlier age without being the primary cause of the lesion. This hyperlipemia may disappear with increasing age after the atherosclerosis is well developed.

SUMMARY

Plasma lipoids were studied in a series of 73 cases of arteriosclerosis obliterans without diabetes mellitus and compared with a control series of 200 individuals of various ages who were considered normal. The ranges of the various lipid fractions and total lipoids were essentially the same in the two groups. However, the mean values for all fractions and for total lipoids were definitely and significantly higher in the patients with arteriosclerosis than in the control group. Since the plasma lipoids have been shown to be essentially normal in thrombo-angiitis obliterans, it is felt that high values for plasma cholesterol and total lipoids may be of diagnostic significance in cases where the differentiation between thrombo-angiitis ob-

literans and arteriosclerosis obliterans is difficult. By the use of diets containing only small amounts of animal fat it was possible to lower the levels of the plasma lipoids definitely in four out of eight cases of arteriosclerosis obliterans where these levels were comparatively high. Three cases have been observed where there was the combination of arteriosclerosis obliterans, xanthoma tuberosum of the skin and marked lipemia.

REFERENCES

1. ANITSCHKOW, N. N., and CHALATOW, S.: Ueber experimentelle Cholesterinsteatose und ihre Bedeutung für die Entstehung einiger pathologischer Prozesse, *Centralbl. f. allg. Path. u. path. Anat.*, 1913, xxiv, 1-9.
2. BAILEY, C. H.: Atheroma and other lesions produced in rabbits by cholesterol feeding, *Jr. Exper. Med.*, 1916, xxiii, 69-84.
3. BLOOR, W. R.: The determination of cholesterol in blood, *Jr. Biol. Chem.*, 1916, xxiv, 227-231.
4. BLOOR, W. R., and KNUDSON, ARTHUR: The separate determination of cholesterol and cholesterol esters in small amounts of blood, *Jr. Biol. Chem.*, 1916, xxvii, 107-112.
5. BLOOR, W. R.: The determination of small amounts of lipid in blood plasma, *Jr. Biol. Chem.*, 1928, lxxvii, 53-73.
6. COWDRY, E. V.: Arteriosclerosis; a survey of the problem, 1933, The Macmillan Co., New York.
7. DAVIS, D., STERN, B., and LESNICK, G.: The lipid and cholesterol content of the blood of patients with angina pectoris and arteriosclerosis, *ANN. INT. MED.*, 1937, xi, 354-369.
8. HUBER, M. J., BROUN, G. O., and CASEY, A. E.: Prevention of cholesterol arteriosclerosis in the rabbit by use of pancreatic extract (lipocaic), *Proc. Soc. Exper. Biol. and Med.*, 1937, xxxvii, 441-445.
9. IGNATOWSKI, A. S.: Quoted by ANITSCHKOW, N. N., and CHALATOW, S.¹
10. LANDÉ, K. E., and SPERRY, W. M.: Human atherosclerosis in relation to cholesterol content of the blood serum, *Arch. Path.*, 1936, xxii, 301-312.
11. LEARY, TIMOTHY: Atherosclerosis. Special consideration of aortic lesions, *Arch. Path.*, 1936, xxi, 419-458.
12. LEARY, TIMOTHY: Atherosclerosis; etiology. Criticisms of experimental evidence pointing to cholesterol, *Arch. Path.*, 1936, xxi, 459-462.
13. LEARY, TIMOTHY: Experimental atherosclerosis in the rabbit compared with human (coronary) atherosclerosis, *Arch. Path.*, 1934, xvii, 453-492.
14. MJASSNIKOW, A. L.: Klinische Beobachtungen über Cholesterinämie bei Arteriosklerose, *Ztschr. f. klin. Med.*, 1925-1926, cii, 65-78.
15. MONTGOMERY, HAMILTON, and OSTERBERG, A. E.: Xanthomatosis. Correlation of clinical, histopathologic and chemical studies of cutaneous xanthoma, *Arch. Dermat. and Syph.*, 1938, xxxvii, 373-401.
16. OCHSNER, H. C., and CONNOR, H. M.: Lipemia accompanied by atheromatous and occlusive vascular disease; report of case and partial review of literature, *ANN. INT. MED.*, 1936, x, 258-269.
17. ROTH, GRACE M., MACLAY, ELIZABETH V., and ALLEN, E. V.: Blood in thromboangiitis obliterans, *Arch. Int. Med.*, 1938, lxii, 413-422.
18. TURNER, K. B., and STEINER, A.: A long term study of the variations of serum cholesterol in man, *Jr. Clin. Invest.*, 1939, xviii, 45-50.
19. WACKER, L., and HUECK, W.: Ueber experimentelle Atherosklerose und Cholesterinämie, *München. med. Wchnschr.*, 1913, ix, 2097-2100.
20. YOUNGBURG, G. E., and YOUNGBURG, MAMIE V.: Determination of lipide phosphorus (lecithin). In: HAWK, P. B., and BERGEIM, OLAF: Practical physiological chemistry, ed. 11, 1937, P. Blakiston's Son & Co., Philadelphia, p. 449.

MUCOSAL CHANGES ACCOMPANYING GASTRIC ULCER: A GASTROSCOPIC STUDY *

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THIS study represents 317 gastroscopic observations on 91 patients, each of whom presented a definite, benign gastric ulcer. Many of these patients were examined repeatedly, as many as 27 gastroscopies being done on one case. No case of ulcer in the postoperative stomach has been included, since we did not wish to analyze mucosal changes, which might be influenced by the trauma incidental to surgery.

We used the Wolf-Schindler flexible gastroscope, in most cases the model with a 50° angle of vision, which provides greater magnification than the 85° instrument and facilitates the observation of very slight changes in the gastric mucous membrane.

Two types of mucosal alteration were found:

I. *Inflammatory Changes.* Gastritic changes range from reddening, edema, and exudation of the superficial type, to the segmentation, node-formation and erosive changes in the hypertrophic form. Atrophic gastritis with a thinned, gray or gray-green mucous membrane and visible, branching blood-vessels may occasionally be found in the ulcer-bearing stomach.^{1, 2}

II. *Purpuric Changes.* This term has been adopted for convenience, to designate mucosal hemorrhages, pigment spots and hemorrhagic erosions. Such lesions are easily recognizable in the gastric mucous membrane. Mucosal hemorrhages are discrete, round or irregular, varying in size from 1 to 5 mm. Occasionally they appear as streaks not over 1 cm. long and 2 to 3 mm. wide. Pigment spots, round or star-shaped and dark-brown in color, frequently accompany and apparently develop from the mucosal hemorrhages. Unabsorbed hemorrhages probably result in the hemorrhagic erosion which is small, but deep, and red, grayish-red or brownish-red in color.^{1, 2} So similar are these lesions to the lesions of the skin and of the mucous membranes (especially of the gastric mucous membrane) in the purpuric diseases, that the term "localized gastric purpura" has been applied.³

The relationship between the acid gastric juice and ulcer has been well studied. Also, the association of inflammation and ulcer has received some attention. However, not until the development of the flexible gastroscope

* Received for publication August 26, 1938.
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has it been possible to observe the progression and regression of mucosal changes. An analysis of the associations thus observed may be helpful in eliminating some of the obscurity surrounding the etiology of gastric ulcer. It is with this thought that this statistical study is presented.

RELATIONSHIP BETWEEN CHRONIC GASTRITIS AND GASTRIC ULCER

Konjetzny⁴ and other European workers who have made studies of resected specimens contend that all specimens examined show some type of gastritis, notably an antrum gastritis; also, that in 50 per cent of all cases a macroscopically visible, severe ulcerative antrum gastritis is present. As will be shown, it is difficult to reconcile our gastroscopic observations with these studies. We will not attempt to explain the discrepancy in this paper. Gastroscopic literature is sparse concerning the subject. Gutzeit⁵ states that rarely is gastritis not seen in ulcer cases and when absent he assumes it to be present histologically. On the other hand he states that he has never seen a case in which a gastritic ulceration changed into a true ulcer. Henning⁶ writes that in his experience, ulcer and gastritis are frequently associated. Moutier,⁷ more in agreement with this study, says, "According to our observations the ulcer usually does not develop from an ulcerative gastritis and one could consider such findings always to be secondary." These authors have not furnished statistics to substantiate their impressions.

A. In this series 43 patients or 47.2 per cent (chart 1) presented no evidence of gastritis at any examination. It must be noted that the diag-

CHART I
Presence or Absence of Inflammation In Ulcer-Bearing Stomachs

	Number	Per Cent
Absent at all examinations	43	47
Absent at first examination. Present at subsequent examinations	10	11
Present at first examination	38	42

nosis of gastritis was made even when the findings were very slight. Even so, the objection might be entered that gastroscopy does not reveal minimal changes. As evidence against this objection the following is cited: A patient was observed in whom deep roentgen-ray therapy to the stomach had been instituted. Gastroscopy revealed a definite but slight superficial gastritis, characterized by patches of adherent exudate. This patient died from coronary occlusion. The histological report read as follows: "Sections of the stomach from many areas reveal slight interstitial infiltrate of inflammatory cells with polynuclears and eosinophiles. Some of these fill the glands. A few bizarre, atypical, epithelial cells, mitoses, and multinucleated elements are seen at the level of the gland necks; particularly in the

section from the anterior wall of the body. These changes may be related to irradiation." The diagnosis was slight acute gastritis, thus confirming the gastroscopic diagnosis. Apparently then, the 50° angle gastroscope permits the diagnosis of gastritic changes of fine degree.

However, even such fine changes were not present in this group of patients. This brings up the possibility that these cases were examined during a regressive phase of the inflammation. Considering that many of these patients were examined on more than one occasion, and that no examination revealed any inflammation, this latter possibility seems unlikely.

Thus in these patients it was not possible to establish a definite relationship between the ulcer and inflammation.

B. An additional 10 patients or 11 per cent (chart 1) showed no evidence of gastritis at the first examination, but did at some subsequent examination. This sequence of events, namely, ulcer followed by inflammation, might be considered circumstantial evidence that the inflammation was incidental to the ulcer. The fact that gastritis did occur eventually, again brings up the possibility that the first examination, revealing an ulcer, might have taken place while the inflammation was in a temporarily regressive stage. Hence, we are deterred from making any statement concerning the relationship in these 10 patients, even though the order of events is highly suggestive. This group will be mentioned again.

C. A group of 38 patients or 42 per cent remains. All of these presented inflammation associated with ulcer. The priority of either could not be determined, so the cases were divided into three groups, based on the proximity of the inflammation to the ulcer (chart 2).

CHART II
Location of the Inflammation With Regard to the Ulcer

	Number
Diffuse	12
Remote	16
Adjacent	10

1. Sixteen cases (or 18 per cent of the total series) presented evidence of inflammation which was entirely remote from the ulcer. It seems inconceivable that the gastritis in these cases could be a factor in the formation of the ulcer, since in each case the ulcer area and the inflammatory area were separated by normal mucosa. There are two, more likely, explanations. First, since the incidence of gastritis was found to be 41.8 per cent in a total of 1000 patients examined gastroscopically, in these ulcer cases it might be purely a coincidental association. Second, the gastritis could quite easily be secondary to the ulcer as a result of food retention, therapy, etc.
2. In 10 cases (or 11 per cent of the total series) the ulcer was found

lying in a zone of inflammation which was circumscribed, but which varied in extent from a narrow, surrounding areola to an area of considerable diameter. In any of these cases it is quite possible that an ulcer developed on an inflammatory basis, but it is just as possible that the reverse could be true and that in some way the ulcer initiated the inflammation. We described previously 10 cases showing no inflammation at the first examination, then subsequently developing inflammatory changes. It is interesting to note that 8 of the 10 developed just such a surrounding gastritis.

3. Twelve cases (or 13 per cent of the total series) presented a diffuse inflammation involving extensive areas of the fundus or of both the fundus and antrum. One can easily consider that an ulcer might develop on such a soil. It is true that shallow erosions do occur frequently in areas of severe inflammation, but such erosions are distinctly different from a true ulcer, being neither demonstrable by roentgen-ray nor possessing the element of chronicity. They are distributed irregularly and appear and disappear with equal rapidity, quite unlike the true chronic ulcer.

Konjetzny remarks on the intimate association between ulcer and ulcerative antrum gastritis in resected specimens. In this entire series of 91 cases, in only 12 instances was an antrum gastritis observed and not one single instance of an ulcerative antrum gastritis. This type of inflammation is readily visualized gastroscopically and has been observed as a separate disease, but it has not been discovered in association with gastric ulcer.

The predilection of ulcer for the lesser curvature is well known. But, if inflammation is a precursor of ulcer and the inflammation is diffuse, we might expect to find a more general distribution of ulcer in the diffuse cases at least. Chart 3 shows the location of the ulcer in each of these 12 cases

CHART III
Location of the Ulcer in the Cases Presenting Diffuse Inflammation

	Number
Lesser curvature	10
Near lesser curvature on posterior wall	1
Posterior wall	1

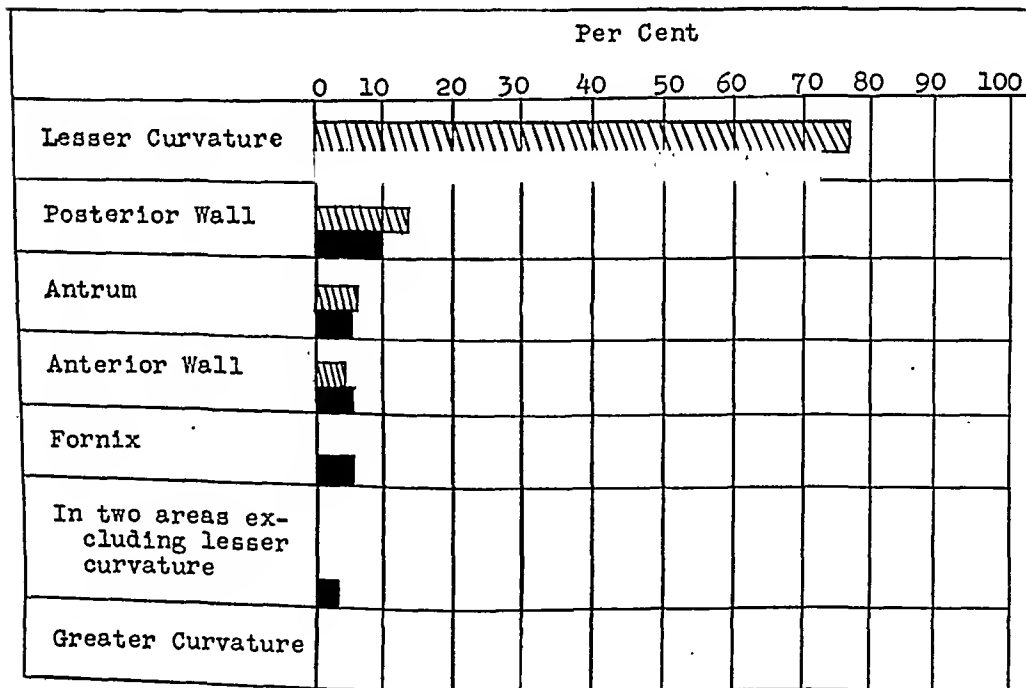
of diffuse inflammation. It is evident that, although the inflammation involved large areas of the stomach, in only one instance was the ulcer found at any appreciable distance from the lesser curvature.

Relationship Between Purpuric-Type Lesions and Gastric Ulcer. In this series, purpuric-type lesions were found in 40 of the 91 cases, an incidence of 44 per cent. When it is considered that in 1000 patients, not suffering from gastric ulcer, these lesions were found in only 5.6 per cent, it

CHART IV
Location of Purpuric Lesions

	Number	Per Cent
Lesser curvature only	15	37.5
Lesser curvature and also in some other area	14	35.0
Posterior wall only	4	10.0
Antrum only	2	5.0
Anterior wall only	2	5.0
Fornix only	2	5.0
In two areas excluding lesser curvature as one	1	2.5
Greater curvature only	0	0.0

CHART V
Illustrating Parallelism between the Purpuric Lesions and the Ulcers



Ulcer location in this series.



Location of purpuric lesions.

becomes very difficult to refrain from attaching some significance to the greater frequency in ulcer-bearing stomachs. The association of ulcer and purpuric lesions in stomachs, in which the mucous membrane is otherwise perfectly normal, is impressive. Even so, the picture may not be complete, since it is possible that, in the cases presenting no abnormality except the ulcer, the formation of this ulcer might have obliterated an initiating mucosal hemorrhage.

Chart 4 shows the location of these lesions in the 40 cases in which they were discovered. In 15 instances they were found on the lesser curvature only, and in 14 additional cases, combined on the lesser curvature and in some other area as well. In four cases, they were found on the posterior wall only and twice each in the antrum, anterior wall and fornix. On one occasion only, two areas of the same stomach other than the lesser curvature were involved.

Chart 5 shows the parallelism between the ulcer location in this series and the location of the purpuric lesions. Cases in which the lesions were found on the lesser curvature only, and those in which the lesions were multiple, being found on the lesser curvature and in some other area as well, were grouped together. The close relationship between the distribution of these purpuric lesions and the distribution of the ulcers is evident.

Theoretical considerations and the available experimental evidence concerning the pathogenesis of these purpuric lesions will not be discussed here. The interested reader is referred to articles by Castex,^{8, 9} Cushing,¹⁰ Burdenko and Mojilnitzki,¹¹ Watts and Fulton,¹² Hoff and Sheehan,¹³ and Schindler.¹⁴

SUMMARY

1. A gastroscopic study of 91 cases of gastric ulcer is presented, dealing with the relationship between certain mucosal changes and ulcer.

2. An analysis of the association of gastritis with ulcer revealed 43 patients in whom no gastritis was discovered, 10 in whom gastritis was not present at the first examination but did appear at some subsequent examination, and 38 in whom both gastritis and ulcer were found at the first examination. The theoretical aspects of these findings are discussed.

3. Purpuric-type changes were discovered in 40 patients. This incidence (44 per cent) is compared with the incidence of such changes (5.6 per cent) in stomachs, not ulcer-bearing. A parallelism between the location of these lesions and the location of ulcer has been found to exist.

BIBLIOGRAPHY

1. SCHINDLER, RUDOLF: *Lehrbuch und Atlas der Gastroskopie*, 1923, Lehmann, Munich.
2. SCHINDLER, RUDOLF: *GastroscoPy—the endoscopic study of gastric pathology*, 1937, University of Chicago Press.
3. CHEVALLIER, PAUL and MOUTIER, FRANÇOIS: *La gastroscopie dans les maladies du sang*, Le Sang, 1937, xi, 935.

4. KONJETZNY, G. E.: Die entzündliche Grundlage der typischen Geschwürbildung in Magen und Duodenum, 1930, Julius Springer, Berlin.
5. GUTZEIT, KURT, and TEITGE, H.: Die Gastroskopie, Lehrbuch und Atlas, 1937, Urban and Schwarzenberg, Berlin and Vienna.
6. HENNING, NORBERT: Textbook of gastroscopy, Translated by H. W. Rodgers, 1937, Oxford University Press, London.
7. MOUTIER, FRANÇOIS: Traité de gastroscopie et de pathologie endoscopique de l'estomac, 1935, Masson et Cie, Paris.
8. CASTEX, M.: Sulla Patogenesi della Porpora emorragica Policlinico, Sez. Med., 1924, xxxi, 509.
9. CASTEX, M.: La pathogénie du purpura hémorragique, Presse Méd., 1924, xxxii, 277.
10. CUSHING, H.: Peptic ulcers and the interbrain, Surg., Gynec. and Obst., 1932, lv, 1.
11. BURDENKO, N., and MOJILNITZKI, B.: Zur Pathogenese einiger Formen des runden Magengeschwürs, Ztschr. f. d. ges. Neurol. u. Psychiat., 1926, ciii, 42.
12. WATTS, J. W., and FULTON, J. F.: The effect of lesions of the hypothalamus upon the gastrointestinal tract and heart in monkey, Ann. Surg., 1935, ci, 363.
13. HOFF, E. C., and SHEEHAN, D.: Experimental gastric erosions following hypothalamic lesions in monkeys, Am. Jr. Path., 1935, xi, 689.
14. SCHINDLER, RUDOLF: Chronic localized gastric purpura, Am. Jr. Digest. Dis., 1939, v, 796.

NEOPRONTOSIL (ORAL) IN THE TREATMENT OF CHRONIC ULCERATIVE COLITIS *

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WITH the advent of the various sulfamido compounds into the field of medical therapeutics it seemed reasonable, as we have stated in a previous article, to investigate the effect of these preparations on patients who have chronic ulcerative colitis.

In using the term "chronic ulcerative colitis," we are referring only to the thrombo-ulcerative form of the disease in which destructive and hyperplastic changes occur in the bowel. We felt that such a trial of therapy was justified because it seemed likely that the organism responsible for the disease might be susceptible to the effect of these sulfamido compounds. In a certain group of cases of this disease, there is every evidence of mild infectious changes limited to the distal segments of the large intestine. There is in other cases all of the evidence of severe destructive and active disease with systemic manifestations of severe toxemia. In the later stage of the disease, there is often evidence of great damage to the bowel and at times, damage to the body generally. This present group of cases embodies examples from all of these groups.

Our early brief experience seemed to indicate that sulfanilamide was of benefit in the treatment of chronic ulcerative colitis. However, as we^{1,3} pointed out later, the occasional appearance of moderate to severe toxic manifestations from the drug among patients treated made it necessary to discontinue the medication at times when the clinical status of the disease indicated the necessity for further treatment. This intolerance for the drug seemed definitely increased among many patients who were acutely ill and who had the disease in advanced stages with extensive ulceration of the colon. Then, too, the occurrence of jaundice, followed by the death of two patients who had received only moderate amounts of sulfanilamide in the treatment of chronic ulcerative colitis made us hesitant regarding the use of this drug in this condition, even though the rôle of sulfanilamide in this sequence of events was never definitely ascertained. In addition to these factors, the inherent chronicity of the disease indicated that prolonged treatment would probably be necessary, and it seemed that for this reason there would be still further opportunity to encounter deleterious effects from the drug.

For these reasons, a search was made through the field of chemotherapy for a preparation which might possess a therapeutic effect comparable to that of sulfanilamide and which at the same time would lack those factors

* Read at the New Orleans meeting of the American College of Physicians March 27, 1939.

of toxicity which would prevent its use in the treatment of chronic ulcerative colitis. We^{1,3} have mentioned elsewhere our brief trial of the dimethylated derivative of sulfanilamide which resulted in our subsequent discard of this preparation for the treatment of this condition.

Subsequently it seemed to us that neoprontosil, because of its known therapeutic efficiency and low toxicity, might offer a satisfactory solution of this problem. At that time, however, neoprontosil was available only in a 2.5 per cent solution and was given parenterally. The inherent chronicity of chronic ulcerative colitis and the necessity for long continued use of any therapeutic measure made it apparent that parenteral administration was impractical. Then too, as was shown by Rosenthal and his co-workers,⁹ 85 to 95 per cent of this drug, when given parenterally to experimental animals, was excreted at the end of five hours. Thus, both of these facts made it apparent that under existing conditions, first, only small amounts of neoprontosil could be made available for use and second, that even if repeated injections were feasible, it did not seem possible that effective concentrations of neoprontosil could be maintained satisfactorily in the body for any prolonged period.

A review of the experimental work of Raiziss et al.,⁸ and of that of Rosenthal and his co-workers, working independently, indicated that if the drug could be given orally it would be retained in the body for a longer time and thus would be more slowly absorbed. It seemed that such conditions would allow for a greater concentration and therefore, greater therapeutic efficiency. Experimental work among animals indicated that this increased efficiency occurred with oral administration.

For these reasons, it seemed to us that a clinical trial of neoprontosil (oral) was justified in cases of chronic ulcerative colitis. The early experience with this drug, which was dispensed in powdered form in a capsule, had previously been reported and this led us to believe that further treatment with this preparation was justified.

The dosage employed was similar to that used previously when sulfanilamide was administered in our treatment of patients who had this disease. To the average adult, amounts of 4 to 5.5 gm. of this drug, divided into five equal parts, were given in each 24 hours. In other words, 15 grains (1 gm.) were usually given an hour before each meal, at bedtime (10 p.m.) and at 3:00 a.m. in order to maintain a uniform concentration throughout each 24 hours. Such a course was administered usually for 10 to 14 days. It was found that if the drug is given an hour before the intake of food, most of the gastrointestinal symptoms usually associated with sulfamido compounds will be eliminated.

In many instances in the more stubborn cases, subsequent to such a course, experience has indicated that an additional course in smaller dosage, approximately 2.5 gm. given daily for another 10 to 14 days, is advisable. In the majority of instances, however, a complete rest from the drug for seven to 14 days was prescribed—between each course of therapy. In a

few cases in which the disease seemed particularly recalcitrant to treatment doses of 4 to 5.5 gm. daily were given continuously for a period of 21 to 28 days without any disagreeable effect save for the occasional presence of some sensation of mild fatigue. In general, a procedure of this type was followed in all of these cases for at least the first three months of treatment and then as improvement occurred the daily dosage was reduced and the periods without the drug were lengthened.

In the present paper, we are reporting on our use of neoprontosil (oral) in a series of 48 patients. Of this number, 29 unselected patients form a part of the report, in which major therapy was restricted to neoprontosil alone (group A). In the remaining 19 cases serum or vaccine was used in conjunction with neoprontosil (group B).

For purposes of comparison and to conserve space, in several instances we have used the familiar standard of grading, 1 to 4, 1 denoting minimal and 4 maximal involvement. Thus, in referring to the extent to which the disease has involved the bowel, as revealed by roentgenologic examination, we have referred to involvement of rectum and sigmoid alone as grade 1. Involvement of the large intestine including the rectum, sigmoid and colon as far as the splenic flexure we have called grade 2; involvement to the hepatic flexure, grade 3, and when the entire large intestine was involved we have used the term, grade 4. Grade 4 plus refers to involvement of the entire colon and terminal portion of the ileum. We have used this same form of comparison for grading the degree of severity of the disease. In all of these cases search has been made for other possible causes of the ulceration of the bowel and in every instance stools have been found free of parasites and ova. It should be pointed out that space does not permit a detailed analysis of each case; therefore the several groups are presented in tables 1 and 2.

In these tables the heading "duration of disease, years" fails to express that the disease may have existed intermittently, and that treatment with neoprontosil was carried out only since the time of the exacerbation which preceded admission to the clinic. Some form of therapy on a symptomatic basis or therapeutic agents such as serum or vaccine, had been given to the majority of these patients at some previous time. In some instances, such treatment had been followed by temporary remission of the disease but in every case the disease was active at the time when treatment with neoprontosil was started by us. It is evident that individual variations in the severity of the disease cannot be accurately described. Thus, it is possible to have involvement of the entire large intestine with objective evidence of only moderate activity and at the same time find great variations, in different instances, of the actual clinical severity of the disease. The column "total duration of treatment, months," in the table refers to the period during which these patients were under treatment with neoprontosil. In most instances, this represents a period of two or four weeks at the clinic and subsequent treatment at home. In many instances, the patients lived near

enough so that they could return for observation at intervals of two or four weeks. It can be seen that the patients in group A (table 1), were under treatment and observation for six weeks to 19 months and those in group B (table 2) from four weeks to 12 months. In every instance where possible we have continued therapy with neoprontosil even when the disease appeared

TABLE I
Chronic Ulcerative Colitis: Data on Treatment with Neoprontosil (Oral); 29 Cases

Group A			Duration of disease, yrs.	Daily number of stools with blood	Roentgenologic evidence of extent of involvement of colon	Findings at initial proctoscopic examination			Clinical severity	Total duration of treatment, months	Findings at last examination		
Case	Sex	Age, yrs.				Act-ivity	Con-trac-tion	Bleed-ing			Sympto-matic	Stools daily	Objective
											Clinical status		On proctoscopic examination
1	M	56	8	5-14	4	2	2	3	2	5	Improved	3-4	"Grade 1"
2	M	38	4	10-15	4	3	3	2	2	6	Improved	3	"Activity minimal"
3	F	38	10	4-9	4	2	2	3	2	14	Inactive	1	"Activity minimal"
4	F	30	7	8-10	4	1	1	1	2	3	Inactive	2-3	"Mucosa appears normal"
5	F	37	2	5-11	4	1	0	1	2	5	Improved	2	"Activity minimal"
6	M	47	7	6-8	4	1	1	2	2	4	Improved	5	"Very little activity"
7	M	36	6	6-8	4	2	0	1	2	13	Inactive	1-2	"No ulceration, no contraction, no bleeding"
8	M	23	6	1-6	4	2	2	1	2	2	Improved	2	"Grade 1"
9	F	43	5	3-10	4	1	1	2	2	3	Inactive	1-2	"Activity minimal"
10	M	41	$\frac{1}{2}$	5	4	2	2	2	2	2	Improved		
11	F	44	6	3-8	4	1	1	1	1	2	Unimproved	3-8	
12	F	29	1	4	2	2	0	3	2	7	Inactive	1-2	"Activity minimal"
13	M	49	8	12	2	2	0	2	2	3	Improved	2	"Activity minimal"
14	F	35	1	4-9	1	2	1	1	2	10	Inactive	1	"Grade 1"
15	M	22	4	6-7	1	2	0	3	2	1 $\frac{1}{2}$	Unimproved	6	"Slight ? improvement"
16	M	18	4	2-3	1	1	0	1	2	1 $\frac{1}{2}$	Improved	2-3	"Activity minimal"
17	F	58	28	1-2	1	1	0	2	2	2	Improved	1-2	"Very definite improvement but some evidence of disease"
18	F	29	3	4-8	1	2	0	2	2	8	Inactive	1	"Normal mucosa"
19	M	52	9	4-6	1	2	1	0	2	5	Inactive	1	
20	F	26	2	5-10	1	1	1	1	2	5	Improved	2-3	"Activity minimal"
21	F	30	9	3-15	1	1	1	2	2	19	Inactive	1-2	"Process quiescent"
22	F	61	2	8-10	1	2	2	1	2	17	Improved	6-7	"Grade 1"
23	M	35	$\frac{1}{2}$	2-14	1	1	0	2	2	2	Improved	2-3	
24	M	21	1 $\frac{1}{2}$	2-5	1	1	0	1	1	17	Inactive	2-3	"Activity minimal"
25	M	48	5	2	1	1	1	1	1	8	Inactive	1	"Normal mucosa"
26	F	43	1	1-2	1	2	0	2	1	2	Inactive		"Very slight granulation anterior wall, otherwise negative"
27	F	72	$\frac{1}{4}$	1-2	1	1	1	2	1	2	Unimproved	1-2	"Same as original"
28	M	31	8	6	1	1	2	2	1	2	Inactive	2	"Activity minimal"
29	M	41	11	4	1	1	0	1	1	1	Improved	2	

TABLE II

Chronic Ulcerative Colitis: Data on Treatment with Neoprontosil (Oral) Plus Serum or Vaccine; 19 Cases

Group B			Duration of disease, yrs.	Daily number of stools with blood	Roentgenologic evidence of extent of involvement of colon	Findings at initial proctoscopic examination			Clinical severity	Total duration of treatment, months	Findings at last examination		
Case	Sex	Age, yrs.				Act-ivity	Con-trac-tion	Bleed-ing			Symptomatic	Stools, daily	Objective
											Clinical status		On procto-scopic examination
30	F	21	4	13	4 plus	2	2	1	3	2	Unimproved	1-2	
31	M	21	4	12	4 plus	2	2	2	3	4	Unimproved	10	
32	M	25	4	9	4 plus	1	3	1	3	4	Unimproved	8	
33	M	23	2	12	4 plus	1	3	1	2	6	Unimproved	9	
34	F	17	1 $\frac{1}{6}$	9	4	2	1	2	3	3	Inactive	1	
35	F	25	8	15	4	1	2	1	3	12	Improved	7	
36	M	18	3	12	4	2	2	2	1	2	Improved	4	
37	F	30	2	5	3	1	1	1	1	2	Improved	3	
38	M	27	4	5	3	1	1	1	1	1	Inactive	1	
39	M	42	7	7	2	1	1	2	3	2	Inactive	1	
40	F	24	1 $\frac{3}{4}$	8	2	1	0	2	2	2	Inactive	1	"Normal"
41	M	12	5	6	2	2	2	2	2	3	Unimproved	6	
42	F	38	9	5	2	1	0	2	1	2	Improved	3	
43	F	24	3	9	1	3	0	2	3	2	Inactive	2	"Activity minimal"
44	F	35	2 $\frac{1}{2}$	4-5	1	2	1	1	1	2	Inactive	1-2	
45	F	20	1	10	1	1	0	2	1	2	Improved	3	
46	F	13	3 $\frac{1}{4}$	14	1	2	1	1	1	1	Inactive	1	
47	M	32	8	2	1	2	1	1	1	2	Improved	1	
48	F	16	1 $\frac{1}{2}$	12	*	3	0	2	3	2	Inactive	2	

* Examination not performed.

quiescent for one or more months. All proctoscopic examinations were made in the Section on Proctology at The Mayo Clinic.

In the analysis of the data obtained from a study of the results of treatment, the following classification of final results has been adopted. Three major groups of results appear in the analysis: (1) The group of cases in which the results could be considered excellent; (2) the group in which the results could be considered fair and (3) the group in which the results were considered poor or unsatisfactory.

ANALYSIS OF GROUP A

Group A was composed of 29 patients who received neoprontosil only. Of the patients in this group 15 were males and 14 females. The youngest patient was 18 years of age, the oldest 72 years of age; the average age was 39.4 years. Thirteen patients (44.8 per cent) obtained results which could be classified as excellent; 13 patients (44.8 per cent) obtained results which could be considered fair and only three patients (10 per cent) obtained results which were considered poor.

He became progressively worse exhibiting marked anorexia, weight loss, profound weakness, and severe dyspnea. From time to time, many petechiae appeared over the skin of his body. During the third week, his venous pressure in the right arm was 10.5 cm. of blood. He developed pulmonary congestion, and the liver became



FIG. 1. Vegetation aortic valve from which brucella were isolated in pure culture.

Note herniation in center of vegetation.

enlarged and tender. He perspired profusely. He suddenly became apprehensive, markedly orthopneic, and expired shortly thereafter. The postmortem examination was done four hours after death. There was slight edema of the feet and eyelids. A petechia was present in the right conjunctiva, and numerous ones over the anterior surface of the trunk and arms. The peritoneal

prostrated. The eyes, ears, nose, and mouth showed no abnormalities. There were prominent pulsations of the neck veins. There were no abnormal findings in the lungs. The apical impulse of the heart was very prominent in the fifth interspace, 12.5 cm. to the left of the mid-sternal line. The sounds were regular, and of good quality. There was a presystolic murmur at the apex with a snapping first sound, which was followed by a loud systolic murmur. Over the aortic area a systolic murmur was heard, and a suggestive systolic thrill was felt. To the left of the sternum in the third interspace, there was a diastolic murmur. The blood pressure was 145 mm. of Hg systolic and 60 mm. diastolic. He had a water-hammer type of pulse. The abdomen was soft showing evidence of marked weight loss. The liver edge was not palpable. The spleen was firm, non-tender, and the edge was felt 3 cm. below the costal margin. No ascites was demonstrated. There was no edema of the extremities, and there were no abnormal neurological findings.

The admission diagnoses were: (1) chronic brucellosis; (2) aortic insufficiency on a rheumatic basis; (3) mitral stenosis and insufficiency, or a functional Austin Flint murmur; (4) brucella endocarditis?

Laboratory findings showed the urines to have a specific gravity of 1.010 to 1.018. Albumin and sugar were absent, and only an occasional leukocyte was present in the sediment. The hemoglobin was 58 per cent (Sahli, 17 grams per 100 c.c. = 100 per cent) on entry. There were 2,600,000 red blood cells and 2,600 white blood cells per cu. mm. The differential count showed 69 per cent polymorphonuclear neutrophils, 30 per cent lymphocytes, and 1 per cent monocytes. Thereafter, the hemoglobin level varied between 75 per cent, and 66 per cent, and the erythrocytes from 2,200,000 to 3,800,000 per cu. mm. A leukopenia was constantly present. The sedimentation rate of the erythrocytes was two mm. in two hours on entry (Westergren method); 36 mm. in two hours, one week later; and the third week after entry, 40 mm. in two hours. Wassermann, Kline, and Kahn tests done with blood serum gave negative reactions. Agglutination tests on the blood for *B. typhosus*, *B. para-typhosus* A and B, and *B. tularensis* were negative on two occasions. The Weil-Felix reaction was absent. Agglutinins for *B. abortus* were present in the blood in a dilution of 1 to 5,120 on three occasions. A culture of venous blood in veal infusion broth made soon after entry remained sterile. In culturing the blood subsequently, special media were employed. Ten c.c. of blood were added to a flask containing 100 c.c. of liver infusion broth. The flasks were placed in a closed jar containing a 10 per cent concentration of carbon dioxide. The flasks were incubated at 37.5° C. for several days, before examining them for growth. Seven blood cultures made in this manner were sterile at the end of 30 days. Two guinea pigs injected subcutaneously with the patient's blood, showed no evidence of brucellosis at the end of three weeks, and six weeks respectively.

Roentgenological examination of the chest showed cardiac enlargement of the aortic type, with no evidence of a mitral deformity. Fluoroscopic examination of the patient's heart and great vessels by Dr. Phillip Hallock revealed a small pulsation of the aorta with a left ventricular type of cardiac enlargement. These findings suggested the presence of aortic stenosis. No mitral deformity was observed.

An electrocardiogram showed left axis deviation, with slurring or notching of QRS in all four leads, which was suggestive evidence of myocardial damage.

The patient was under observation for 27 days before he died. All during this time, his temperature varied between 99° and 102° F., and was usually elevated in the afternoon. His pulse rate was between 90 and 110 beats per minute. Shortly after entry a skin test was done with the same suspension of brucella organisms used in the agglutination test by the Minnesota Department of Health. No demonstrable reaction was present in 24 and 48 hours. He was given six transfusions of citrated blood. A few days after entry, petechiae of the buccal mucous membrane were noted, and in the second week, a small hemorrhage was observed in the sclera of the right eye.

culture of brucella recovered from the vegetations, produced the characteristic lesions of brucellosis when injected into a guinea pig. The second case is that of Rothman⁴ and concerns a 61 year old male who complained of anorexia, fever, and loss of weight. His blood serum agglutinated *Brucella melitensis* var. *melitensis* in a titer of 1 to 800. A soft systolic murmur was detected over the precordium. The patient died suddenly, and postmortem examination revealed marked destruction of the aortic valve with fresh vegetations present. The abortus strain of brucella was isolated in pure culture from the vegetation, as well as from the kidney, spleen, liver and blood. A brucella infection was established in guinea pigs with the organisms obtained from the aortic vegetations. There are several other cases reported where precise bacteriological data obtained at necropsy are lacking, but in which there is sufficient clinical and pathological evidence to warrant a probable diagnosis of brucella endocarditis. In the reports to be cited, there are no statements that brucella were isolated from the valves at autopsy, and identified by cultural and serological methods. We may include in this group, reports in this country by de la Chapelle,⁵ and Levy and Singerman⁶ who have each presented a case of endocarditis said to be due to *Brucella melitensis* var. *melitensis*. Hardy and his associates⁷ in an excellent summary of the clinical findings in 300 cases of brucellosis occurring in Iowa included one case of endocarditis due to brucella of porcine origin. Gonnella and Warter⁸ in France, described a case of vegetative endocarditis with *Brucella melitensis* var. *melitensis* as the probable cause. Rennie and Young,⁹ in England, concluded that an abortus strain of brucella was the cause of malignant endocarditis in a case studied by them.

CASE REPORT

A 29 year old white farmer residing in Minnesota entered the University Hospital complaining of weakness, loss of weight, and fever. Seven months before entry, he had a swelling of the great toe on the right foot. At the same time, he had anorexia and a cough productive of blood-tinged sputum. After remaining in bed for two weeks, he recovered sufficiently to work, but during the following two months, collapsed several times in the fields. Five months before entry, he was suspected of having hyperthyroidism because of a slight swelling of his neck in the region of the thyroid gland. His basal metabolism was found to be plus 45 per cent, and iodine solution was administered without relief of his symptoms. Three months before entry, he had chills for the first time. One month later his physician heard a systolic murmur over the apex, which had not been present on previous examinations. At this time, an agglutination test of his blood showed agglutinins present in a titer of 1 to 2,560 for *Brucella melitensis* var. *abortus*. We were informed later that 50 per cent of the cattle on the farm where he was employed showed evidence of a brucella infection. The patient had drunk raw milk obtained from these cows. One month before entry, he was given 60 to 80 grains of sulphamamide for several days without improvement. He was then given subcutaneously on three occasions 200 c.c. of citrated blood obtained from a donor who had recovered from brucellosis. However, his condition became worse. His temperature fluctuated between 99° and 105° F. Brucella vaccine was administered subcutaneously, but he became progressively worse. Just before entry he had several episodes of nausea and vomiting. His past history revealed no significant details. He had always been in good health until his present illness. He denied having had rheumatic fever, chorea, or a venereal disease. Physical examination showed a well-developed, poorly nourished male, quite

REFERENCES

1. MARIE, P.: Sur deux cas d'acromégalie; hypertrophie singulière non congénitale des extrémités supérieures, inférieures et céphalique, *Rev. de méd.*, 1886, vi, 297-333.
 2. BÉCLÈRE, A.: The radio-therapeutic treatment of tumours of the hypophysis, gigantism and acromegaly, *Arch. Roent.-Ray*, 1909-10, xiv, 142.
GRAMAGNA: Un cas d'acromégalie traité par la radiothérapie, *Rev. Neurol.*, 1909; Quoted by Bécclère.
WEBSTER, J. H. D.: Roentgen ray treatment of a case of early acromegaly, *Arch. Radiol. and Electro-Therap.*, 1920-21, xxiv, 261.
TOWNE, E. B.: Roentgen-ray treatment of pituitary tumors, *Arch. Neurol. and Psychiat.*, 1926, xv, 92.
GALLINO, M. M., and GALLINO, A. A.: Roentgenterapia de los tumores de la hipofisis, *Semana med.*, 1933, ii, 1486-1491.
 3. MEAGHER, R., and HEUER, G. J.: A text-book of medicine, edited by R. L. Cecil, W. B. Saunders Co., Philadelphia, Third Edition, 1935, page 1236.
 4. CUSHING, H.: The pituitary body and its disorders, 1912, J. B. Lippincott Co., Philadelphia, page 235.
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BRUCELLA ENDOCARDITIS *

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BACTERIAL endocarditis due to brucella organisms is an infrequent, but serious complication, that may occur in patients with brucellosis. A review of the literature indicates that many cases have been reported as brucella endocarditis without adequate anatomical or bacteriological proof. In a recent comprehensive review of the pathology of brucellosis due to brucella of bovine origin, Albertini and Lieberherr¹ state that reports of brucella endocarditis are usually instances of brucellosis with a coincidental endocarditis present. This statement is well illustrated by the observations of Scott and Saphir.² They studied a patient who had an aortic and mitral valvulitis of rheumatic origin, but who later contracted brucellosis. *Brucella melitensis* var. *abortus* organisms were repeatedly isolated from the patient's blood. The patient exhibited the characteristics of a fatal course of bacterial endocarditis, but after a postmortem study, they concluded that it was an instance of rheumatic endocarditis associated with a brucella bacteremia.

Our interest in this subject was stimulated by the clinical and pathological studies carried out on a patient with bacterial endocarditis proved to be due to the abortus variety of brucella. We have reviewed the literature for cases of endocarditis caused by the various strains of brucella, and have found only two substantiated by bacteriological and anatomical evidence at necropsy. Casanova and D'Ignazio³ reported the first case in 1933. A 28 year old male with fever developed congestive heart failure and died. Before death, a systolic murmur was heard over the aortic area. Agglutinins for *Brucella melitensis* var. *melitensis* were demonstrated in his blood, and the organism was isolated from his blood. At autopsy, fresh vegetations were found on the aortic valve. A pure

* Received for publication July 25, 1938.

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regularly. The menstrual cycle was normal. No enlargement of the hands or feet had occurred. The blood pressure was 92 systolic, 60 diastolic. The ophthalmoscopic examination and the visual fields were normal.

DISCUSSION

When this patient was first seen there were signs both of tumor pressure and abnormal hormonal activity in association with enlargement of the hypophysis. That prompt beneficial influence was exerted by the roentgen-rays was indicated by the rapid subsidence of headache, the disappearance of evidence of pressure on the optic tracts, and the return of a normal sense of smell. The late effects were remarkable and not altogether anticipated. There was no evidence of progressive change in the skeletal system. This we had hoped for. The return of the blood sugar and basal metabolic rate to normal levels was noteworthy. The reestablishment of the menstrual cycle was more than we expected and the occurrence of pregnancy seven years after irradiation of the pituitary region was quite unpredicted.*

It is rather unusual, as judged from other reports,² to have such striking improvement occur in acromegaly after roentgen-ray treatment. It should be remembered that spontaneous remissions are known to take place.³ However, the decided improvement observed in this patient followed so soon after the roentgen-ray treatment and was in such marked contrast to the progressive downward course of the disorder up to the time of treatment that a causal relationship between treatment and improvement seems highly probable. Moreover, if a spontaneous remission had occurred in 1928 it seems likely that during the ten years which followed some evidences of hypopituitarism might have become evident. Instead there seems to have been established a satisfactory balance. It appears that overactivity of the gland ceased entirely and the functions which had been suppressed prior to roentgen-ray treatment subsequently reached and maintained a normal level of activity.

It is of interest that during the course of the pregnancy no abnormal functional activity of the pituitary was observed. The onset of acromegaly and the activation of the disorder during pregnancy have been noted.⁴ In the treatment of acromegaly uncomplicated by rapidly failing vision it may be desirable, in the light of our experience, to use deep roentgen-ray therapy in every instance whether or not signs of hypophyseal tumor are impressive. In some instances it may be then possible to avoid surgical treatment; in others, operative treatment may be delayed without detriment to the patient.

SUMMARY

A white woman, now 40 years old, developed in 1922 symptoms and signs of acromegaly. The evidence of hypophyseal tumor was impressive enough in 1928 to indicate treatment. This treatment consisted of deep roentgen-rays. The result was brilliant. Most of the symptoms were relieved and, after a childless marriage of 10 years' duration, the patient gave birth to a healthy infant in 1936. The size of the skeleton has not altered materially in 10 years.

* It is true that we do not know that her husband has had normal spermatozoa all these years, and since he refuses to cooperate with us, information relating to the present state of his spermatic fluid is not obtainable.

been less nervous and had not suffered with headache. There had occurred no visual disturbances and the sense of smell had been normal. No change in the size of her gloves or shoes had occurred.

In 1932 she experienced the return of libido. Her menstrual cycle became re-established and was in every way normal.

In August 1933 she was readmitted to the hospital because of acute bronchitis. There was no evidence of any progression in the skeletal abnormalities. The basal metabolic rate was minus 3 per cent.

In February of 1935, she was seen in the endocrine clinic because of amenorrhea of three months' duration. The uterus was found to be slightly enlarged. Roentgen-rays made at this time showed widening and tufting of the ends of the phalanges of all the fingers. There was no essential change in the sella turcica. The visual fields and acuity were normal. A few weeks later she fell and a miscarriage occurred. In April 1935 she had a normal menstrual period. In August 1935 she visited the obstetrical clinic because she had failed to menstruate since May. She was found to be pregnant. She returned at regular intervals to the obstetrical clinic and was observed throughout a normal pregnancy. She was admitted to the Vanderbilt Hospital on February 25, 1936, and, after a fairly difficult labor because of a posterior position, was delivered of a normal male infant. The baby weighed eight pounds and 10 ounces, and breathed spontaneously. The puerperium was normal.

The patient was examined in April 1937 and there was no evidence of any progression in the pituitary disorder. (Figure 3.) The findings on physical examination were essentially unchanged. The blood pressure was 94 systolic and 66 diastolic, the basal metabolic rate was minus 1 per cent, the visual fields were normal and the urinalysis was negative. Blood chemistry studies were as follows: Non-protein nitrogen 24 mg. per cent; uric acid 2.5; cholesterol 172; phosphorus 3.95; calcium 9.6; sugar 100; the total serum proteins were 6.62 grams per cent with an albumin fraction of 4.40. She reported that she felt well and worked regularly, and that her menstrual periods were perfectly normal.

In February 1938, at the time of her last visit to the clinic, no significant changes were noted. (Table 1.) Her health had remained excellent, and she had worked

TABLE I

Measurements made during period October 1929 to February 1938. The head and chest measurements were made with a pelvimeter and are expressed in centimeters.

	Oct. 1929	Feb. 1935	April 1937	Feb. 1938
<i>Head</i>				
Anterior-posterior of skull	19	20	21	20.5
Tip of chin to vertex of skull	25.5	25	26.5	26
Mastoid to mastoid	14	15	14	14
Zygoma to zygoma	14	14	13	14
Tip of chin to hair-line	20	20	20	20
Tip of nose to hair-line	12	12	11	11
Tip of nose to external occipital protuberance	23.5	24	23	23.5
Lateral angle of mandible to opposite mandible	11	11	11	11
<i>Chest</i>				
Anterior-posterior at level of xiphoid	24	22	22	21.5
Anterior-posterior at fifth costo-sternal level	26	24	25.5	25
Anterior-posterior at third costo-sternal level	25	24	24	23
Anterior-posterior at supra-sternal notch	18	18	18	17
Transverse at superior axillary levels	25	26	25	26
<i>Trunk</i>				
Height	162.6	165.1	163.2	162.6
Upper measurement		83.8	82.6	81.3
Lower measurement		81.3	80.6	81.3
Weight (kilograms)	61.4	70.7	65.9	69.1



Fig. 3. Photograph of patient, April 1937, with her 14 month old son.

when compared with the films of May 1928. Although there were no positive indications for further roentgen-ray treatment she was given empirically a fifth and final treatment of approximately 1,000 'R' on September 18, 1929.

During the next four years the patient appeared in the out-patient department with minor ailments. She was working and apparently felt greatly improved. She had

The red blood cell count was 4,880,000, the hemoglobin 93 per cent (Sahli). The white blood cell count was 7,850 of which 57 per cent were neutrophils, 37 per cent lymphocytes and 6 per cent monocytes. The blood Wassermann test was negative.

The basal metabolic rate was plus 17 per cent.

A glucose tolerance test was performed using 1.5 grams glucose per kilo of weight: the fasting blood sugar was 114 mg. per cent, after one hour 142, two hours 133, three hours 86, four hours 80, five hours 78. All urine specimens collected during this period gave negative tests for glucose.

Roentgenograms of the skull revealed marked enlargement of the sella turcica with hypertrophy of the posterior clinoid process. (Figure 2.) No changes were



FIG. 2. *a*. Roentgenogram, 1928, showing marked enlargement of the sella turcica and hypertrophy of the posterior clinoid processes. *b*. Roentgenogram, 1938, showing no significant change from the 1928 film.

noted in the bones of the hands and feet. All the sinuses and especially the frontals were large. The chest plate revealed no abnormalities.

It appeared evident that the patient had an adenoma of the pituitary with acromegaly and there was evidence of pressure on the optic chiasma and dysfunction of the left olfactory tract. It was decided to treat her by means of roentgen-rays and accordingly on May 2, 1928 she was irradiated over the pituitary region. The treatment consisted of 20 milliamperes for 15 minutes through a $\frac{1}{2}$ millimeter copper and one millimeter aluminum filter. This was delivered through an 8 centimeter portal at a distance of 50 centimeters. The roentgen-ray machine was a 200,000 volt apparatus, and the dose delivered was 300 milliamperere minutes, amounting to approximately 800-900 'R' (with "back-scatter"). This treatment was given on each of two successive days in April and on June 28 and June 30, 1928 the treatment was repeated. Following these roentgen-ray treatments the patient felt definitely improved.

She was re-admitted to the hospital in October 1929 for the removal of a pedunculated sebaceous cyst of the left leg. In the interval since her last admission she had experienced no weakness, irritability, headache or visual disturbance. On this second hospital admission the physical examination and the laboratory data were essentially unchanged. The basal metabolic rate was now plus 23 per cent. A glucose tolerance test was as follows: The fasting blood sugar was 75 mg. per cent, after one hour 125, two hours 108, and three hours 62. The urine volume for 24 hours was 2,910 c.c. The visual fields were essentially normal. The visual acuity was 20/20 in each eye and roentgenograms of the sella turcica showed no change

ache became constant. She localized the discomfort chiefly in and about the left eye. Vomiting had occurred occasionally in association with headache. Her past health had been good. Her father and mother were living and well. She had four siblings. One sister had diabetes. No disease had appeared with unusual frequency in her family.

Physical examination (April 1928): Temperature 98.6° F., pulse 84, height 65.6 inches (166 centimeters), weight 135 pounds (61.4 kg). The facial characters were considered typical of acromegaly. (Figure 1.) The voice was coarse and deep. The



Fig. 1. Photographs of patient made in 1920 and 1928.



mental functions were normal. The fingers were thicker and shorter than normal. The skin was coarse; the hair, while coarse, was normal in distribution. The thyroid was diffusely enlarged. It contained no nodules, and no thrill or bruit was present. Lid lag and slight failure of convergence were noted. The pupils reacted normally. The exophthalmos being more marked on the left. There was no evidence of increased intracranial pressure. There was slight prognathism. The teeth and tongue were normal. The bony thorax was normal save for the changes usually associated with slight emphysema. The heart and lungs were not remarkable. The blood pressure was 105 systolic, 80 diastolic. The abdomen was normal as were the external genitalia. The body of the uterus was quite small. The cervix was normal. The neurological examination revealed normal muscle tone and strength. No vasomotor abnormalities were noted. The deep reflexes were normal as were position and vibration perception. No pathological reflexes were present.

Cranial nerves: there was a marked difference in the sense of smell on the two sides; on the left, neither vanilla, coffee, peppermint nor vinegar could be identified, while on the right side all odors except coffee were recognized and were described as much more intense. Visual acuity was normal but perimetric charts of the visual fields revealed slight, definite temporal constriction. The latter was more pronounced when red and green targets were used. The urine was normal.

CASE REPORTS

THE RESPONSE OF ACROMEGALY TO DEEP ROENTGEN-RAY THERAPY: A CASE REPORT *

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THERE is ordinarily no difficulty associated with the diagnosis of typical acromegaly. Following the classical descriptions by Marie,¹ the disorder became recognized as one of rather frequent occurrence. Nevertheless, the treatment of acromegaly has remained unsatisfactory. Occasionally the underlying pathological changes in the pituitary are such that the symptoms and signs are chiefly those of a space-occupying, hypophyseal tumor. Under such circumstances and especially when vision is threatened by pressure on the optic chiasma, the inclination is to regard and treat the disorder from the view-point of tumor formation rather than hormonal dysfunction. On the other hand, when signs of a space-occupying mass are absent and no involvement of cranial nerves occurs the abnormal constitutional manifestations of hypophyseal dysfunction dominate the therapeutic problem and treatment is non-surgical.

In the patient whose case report follows the symptoms and signs of an intracranial tumor were present in association with manifestations of hypophyseal dysfunction.

CASE REPORT

B. A., a white female, now 40 years of age, first came to the Vanderbilt University Hospital in April 1928. She complained of amenorrhea of six years' duration.

The menarche had occurred at 13; the periods were regular, occurred in a 28 day cycle and were normal in character.

In September 1922, when she was 24 years old, the menses ceased abruptly. In 1926, she first noted changes in the facial characters; the features gradually became coarse, the nose broad, the lips thickened and the eyes more prominent. Her voice became husky. She experienced pains in her fingers and she noted an increase in the size of her hands and feet. She now wore size 9 gloves and size 6 shoes whereas formerly her glove size was 6 and shoe size 3. In 1924 at the time of a tonsillectomy she was told that the thyroid was enlarged. Since that time the gland has not increased in size. Members of her family felt that she had recently become nervous and emotionally unstable. Her appetite had been good though not excessive and she had lost no weight. During 1926 and 1927 she felt exhausted and experienced great difficulty in continuing to work in a shoe factory.

She married in 1926 and her husband was living and well. There had been no pregnancies. Contraceptives had not been used.

For a year prior to admission to the hospital she had experienced frequent headaches which she localized behind the eyes and she had been conscious of eye strain associated with lacrimation. During the month preceding her admission head-

* Received for publication June 6, 1938.

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REFERENCES

1. BANNICK, E. G., BROWN, A. E., and FOSTER, F. P.: Therapeutic effectiveness and toxicity of sulfanilamide and several related compounds: further clinical observations, Jr. Am. Med. Assoc., 1938, cxi, 770-777.
2. BARGEN, J. A.: The management of colitis, 1935, National Medical Book Company, Inc., New York.
3. BROWN, A. E., HERRELL, W. E., and BARGEN, J. A.: Neoprontosil (oral) in the treatment of chronic ulcerative colitis, Proc. Staff Meet. Mayo Clin., 1938, xiii, 561-565.
4. BRUNSTING, L. A., GOECKERMAN, W. H., and O'LEARY, F. A.: Pyoderma (ecthyma) gangrenosum; clinical and experimental observations in five cases occurring in adults, Arch. Dermat. and Syph., 1930, xxii, 655-680.
5. HERRELL, W. E., and BROWN, A. E.: Clinical use of neoprontosil (oral), Proc. Staff Meet. Mayo Clin., 1938, xiii, 555-560.
6. KING, J. T., HENSCHEL, A. F., and GREEN, B. S.: Influence of prontosil-soluble on beta hemolytic streptococci growing in tissue culture media, Proc. Soc. Exper. Biol. and Med., 1938, xxxviii, 810-812.
7. MARSHALL, E. K.: Personal communication to the authors.
8. RAIZISS, G. W., SEVERAC, M., MOETSCH, J. C., and CLEMENTE, L. W.: The chemotherapy of sulfanilamide, prontosil soluble, di-sulfanilamide and prosepasmine, Jr. Chemo-therapy, 1938, xiv, 91-105.
9. ROSENTHAL, S. M., BAUER, HUGO, and BRANNHAM, SARA E.: Studies in chemotherapy. IV. Comparative studies of sulphonamide compounds in experimental pneumococcus, streptococcus, and meningococcus infections, Pub. Health Rep., 1937, lli, 662-671.

of that made possible by absorption of the drug by mucous membranes or by the presence of the drug in the systemic circulation.

It is important to emphasize that experience with chronic ulcerative colitis has shown that it is a disease characterized by spontaneous exacerbations and remissions. We believe, however, that the prompt improvement of these lesions which has occurred so frequently and uniformly after the use of neoprontosil justifies the conclusion that the drug is of definite benefit in this disease. It follows, however, that the tendency of the disease to recur must be appreciated fully in treating this condition. Therefore, in every instance we have continued to give intermittent courses of treatment even when the disease has been symptomatically and objectively inactive for some months. The lack of toxic manifestations associated with the use of neoprontosil in general makes this drug especially adaptable to the treatment of chronic ulcerative colitis.

SUMMARY

A clinical study has been presented in an attempt to evaluate the effectiveness of neoprontosil (oral) in the treatment of 48 patients who had chronic ulcerative colitis. For the purpose of further evaluation of therapy one group comprising 29 patients (group A) received neoprontosil only. Another group of 19 patients (group B) received, in addition to neoprontosil, either vaccine or serum.

It appears that 44.8 per cent of the patients in group A obtained clinical results which could be classified as excellent; that 44.8 per cent obtained results which could be considered fair and that failure of treatment or poor results occurred in only 10 per cent of cases.

The analysis indicates that 42 per cent of patients in group B obtained results which were considered excellent whereas 32 per cent obtained results which may be considered fair. Failure of treatment or poor results occurred in 26 per cent of this group. It should be noted that the two groups are not identical as regards severity of the disease; nevertheless the results seem significant.

It is also of significance that the clinical response to neoprontosil is not predictable on the basis of the amount of bowel involved by the disease so long as destruction of the bowel is not too great.

We are exceedingly anxious not to create the impression that neoprontosil is a specific remedy for chronic ulcerative colitis. However, it is reasonable to deduce from the results herein reported that the lack of toxic manifestations associated with the use of this drug and the comparatively encouraging clinical responses amply justify the use of neoprontosil (oral) in the treatment of chronic ulcerative colitis.

drug. In the entire group of patients the content of hemoglobin, and the number of erythrocytes and leukocytes in the blood did not show any significant untoward changes which could be attributed to the use of neoprontosil. In some instances transfusions were given because of an already existing anemia that resulted from loss of blood or from toxemia. Repeated examination of the urine of these patients did not show evidence of renal irritation attributable to neoprontosil.

It is of interest that the estimation, according to the method of Marshall, of the concentration of sulfanilamide in the blood of these patients while receiving neoprontosil varied as a rule between 0.9 and 3.6 mg. per 100 c.c. of blood and that the average value was 2.4 mg. Although these estimations are lower than those usually encountered among patients receiving similar amounts of sulfanilamide, nevertheless we believe that they constitute definite evidence of the absorption of orally administered neoprontosil. Examination of the urine of these patients showed the presence of free sulfanilamide in concentrations of 46 to 69 mg. per 100 c.c. and conjugated sulfanilamide in concentrations of 31 to 56 mg. per 100 c.c. These estimations of sulfanilamide in the urine also are appreciably lower than those which are found when sulfanilamide is administered in similar doses.

It seems proper at this point to emphasize an observation which we made previously regarding the use of neoprontosil in cases of ulcerative colitis; namely, that it is not possible for any chemotherapeutic agent to restore to normal the physiologic function of a bowel which has become contracted and deformed by the presence of disease of long standing. Obviously under such circumstances all that any such drug can be expected to accomplish is the control of symptoms that are due to active infection; those symptoms which result from altered function of a deformed bowel must be expected to continue to disturb the patient. If, however, neoprontosil is used early in the course of chronic ulcerative colitis, it seems evident that the maximal effect from the drug will be obtained.

At present, only impressions exist concerning the mode of action of neoprontosil in the treatment of chronic ulcerative colitis. Certainly we do not feel that the therapeutic response can be explained on the basis of the sulfanilamide which is made available to the systemic circulation by the breakdown of neoprontosil. In other words, as we have suggested previously, it would appear that neoprontosil possesses an action which is wholly independent of and in addition to that of the sulfanilamide which it liberates. The recent experimental work of King and his co-workers⁹ tends to substantiate this impression. Although the experimental work of Marshall indicates that neoprontosil is not absorbed by the large bowel of animals, it seems likely that this absorption occurs in the large bowel of man. It also seems possible that the mere presence of the drug in direct contact with the mucous membranes of the bowel may exert a local action independent

stuffs occurred. In case 32, there was a very marked secondary anemia with an associated toxemia. General improvement occurred in this case with improvement of the anemia and with a gain of 15 pounds, but little change took place in the symptoms from the bowel. Our experience with other similar cases reveals instances in which the same type of response followed treatment. In case 41, the patient, aged 12 years, had in addition to chronic ulcerative colitis a cerebral lesion, either an abscess or a brain tumor. After some temporary improvement he suffered a subacute perforation of the sigmoid.

COMMENT

In addition to the foregoing clinical appraisal of these cases, there are certain points of general interest in connection with this form of therapy. One of the most important of these is the general lack of toxic manifestations which might be attributed to the use of neoprontosil. This observation in this group of cases of chronic ulcerative colitis is in accordance with the previous experience of Herrell and Brown⁵ with the use of this drug in the treatment of more than 500 patients who had various types of infections. Although minor degrees of malaise, fatigue and headache were noted at times during the treatment of chronic ulcerative colitis with neoprontosil the symptoms were never of a degree sufficient to necessitate withdrawal of the drug and but rarely were of a nature requiring a reduction of the prescribed doses. As aforementioned, general systemic manifestations of intolerance are exceedingly rare in all cases in which neoprontosil is used; however, there is a tendency to local irritation of the bowel; cramps or diarrhea may occur at times when large amounts of the drug are given, for instance amounts in excess of 5.5 gm. daily. We feel that an explanation for this irritation rests on the probability that the bowel is receiving larger amounts of the drug than it is able to absorb and that some local irritation is thereby produced.

We have also encountered a similar effect but a temporary one among certain patients who had chronic ulcerative colitis, particularly those who had involvement of the entire colon with deformity and scarring. In such cases the drug at times produced cramps and exacerbation of the diarrhea but these symptoms promptly subsided when the medication was discontinued. Under a reduced dosage, 2.5 gm. or 3.5 gm. daily, such patients have been able to continue with treatment until material improvement has occurred. Two patients, who were not under our direct observation at the time, experienced a mild rash of questionable type and treatment was discontinued temporarily. Nausea and emesis also occurred temporarily in several cases. Cyanosis did not occur in any of these cases although, occasionally, small amounts of methemoglobin and sulfhemoglobin were detected in the blood by spectroscopic analysis. In no instance was there noted any significant decline of the carbon dioxide combining power of the blood plasma despite the fact that these patients did not receive alkalies with the

tirely healed save for a few minute denuded areas. Proctoscopic examination at this time showed the intestinal mucosa to be entirely normal save for the presence of some scarring (table 2).

ANALYSIS OF GROUP B

Group B was composed of 19 patients who received neoprontosil plus serum or vaccine. Of the patients in this group, eight were males and 11 females; through mere chance these patients were considerably younger than those in group A. The youngest patient was 12 years of age and the oldest, 42 years; the average age was 24.3 years. In eight cases (42 per cent) in this group (cases 34, 38, 39, 40, 43, 44, 46, 48) results were classified as excellent because the disease was symptomatically inactive. In two of these cases subsequent proctoscopic examinations were performed; in one (case 40) the mucosa was healed and in one (case 43), there was minimal activity of the disease.

An opportunity for final proctoscopic examination of the other six patients did not occur. Their condition was improved when they were dismissed from the clinic and subsequent reports revealed that they were free of symptoms. Two of these (cases 34 and 48) deserve special comment, girls of 17 and 16 years of age respectively, who had been severely ill for weeks with marked symptoms of sepsis and toxemia and with temperatures of 104° F. (40° C). Two weeks after the administration of neoprontosil, in the usual manner, their temperatures had receded to normal, the rectal discharges had been greatly reduced and the blood in the stools had diminished to a great extent. It should be noted that whereas involvement of the bowel of one patient was extensive the other patient was too ill for roentgenologic examination. In both cases the duration of the disease was brief but the disease was moderately acute. In case 10 in group A a similar type of disease was present with symptoms of sepsis and a similar response to neoprontosil occurred.

Six (32 per cent) patients (cases 35, 36, 37, 42, 45, 47) obtained results which were fair. That is, they were definitely improved symptomatically but this could not be evaluated objectively because final proctoscopic examinations were not made.

All five patients (26 per cent) (cases 30, 31, 32, 33, 41) who were unimproved had extremely advanced disease. They all showed evidence of severe destruction of the entire large intestine and terminal portion of the ileum, or serious complications of the disease.

In case 30 there was involvement of the entire large bowel and terminal portion of the ileum, nutritional edema and a rectovaginal fistula with other fistulas near the anus. In case 31 there was involvement of the entire large bowel and terminal portion of the ileum and the whole segment was an irregular tube about 1 to 1.5 cm. in diameter. In case 33, in addition to the ulcerative colitis, annoying gastrointestinal allergic manifestations to food-

from the knee to three inches above the ankle, with the exception of an intervening longitudinal bridge of unaffected tissue 5 cm. wide (figure 3). Neoprontosil was again given in doses of 5.5 gm. daily. After five days the temperature and number of leukocytes again returned to normal and the general condition was much improved. The ulcer, however, showed no



FIG. 3. Pyoderma gangraenosum subsequent to use of neoprontosil (oral) showing extent of involvement by ulcer and degree of healing (case 4).

definite evidence of healing over a period of 14 days. During this time the involvement had spread so that the band of previously described intervening tissue had narrowed to 1 cm. Improvement was then noted and the borders of the ulcer lost their inflammatory appearance. Improvement continued in a remarkable manner and at the end of three weeks the ulcer was en-



FIG. 2. *Pyoderma gangraeniosum*. *a*, Before treatment with neoprontosil (oral); *b*, extent of healing after treatment (case 17).

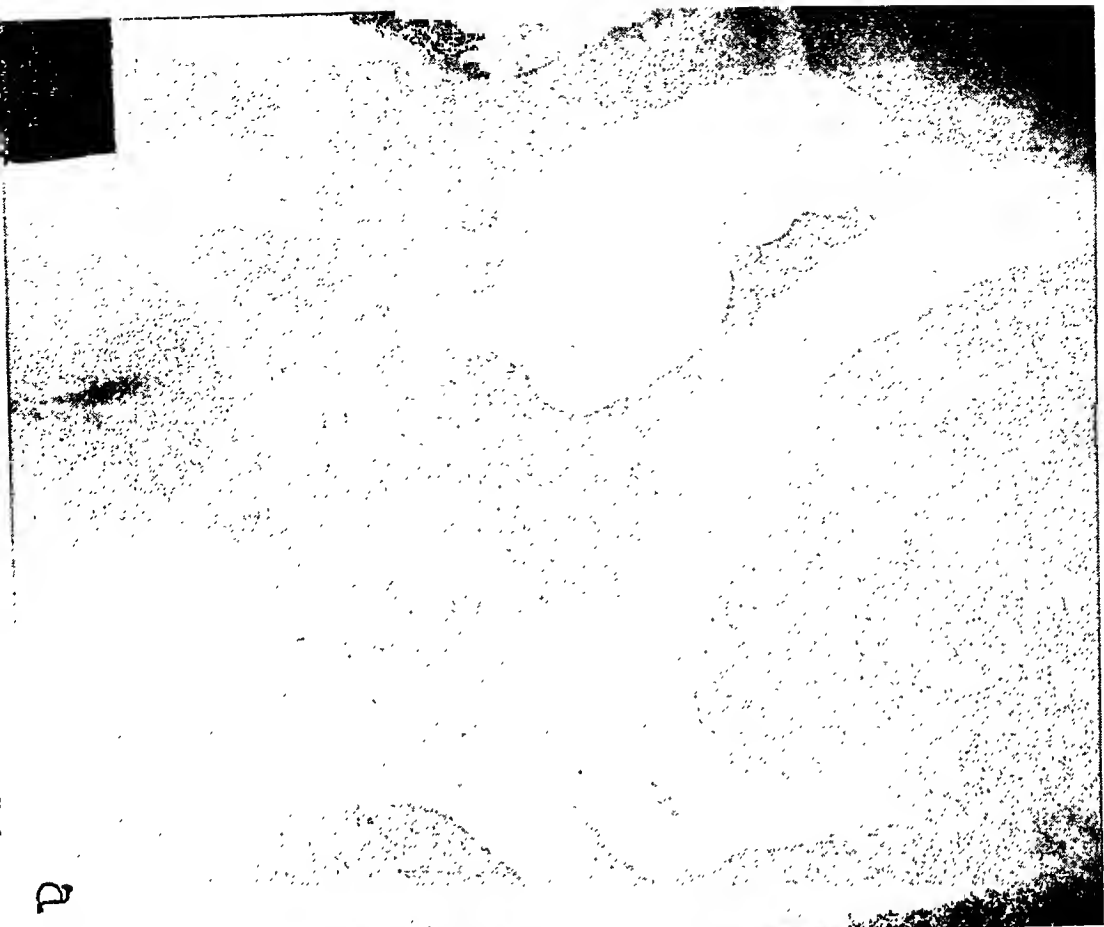
patient (case 4) first noticed an ulcer of the left leg one month prior to admission to the clinic. It occurred after local trauma and an acute respiratory infection. At the time of admission, the ulcer was 3 cm. in diameter and possessed undermined edges; organisms were not recovered from it on culture. The chronic ulcerative colitis involved the entire colon and its activity on proctoscopic examination was graded 1+. The patient's temperature was 102° F. (38.9° C.) and the leukocytes numbered 22,000 per cubic millimeter of blood. After only four days of treatment with neoprontosil plus the use of scarlet red ointment locally, the inflammation in the border of the ulcer subsided and healing occurred. The temperature and the number of leukocytes returned to normal after seven days. After 14 days, healing had progressed to a stage at which it was felt advisable to dismiss the patient.

At this time, treatment with neoprontosil was discontinued for a period of two weeks and during this interval the ulcer of the leg recurred and rapidly increased in size. The patient returned to the clinic five weeks later and again was acutely ill. The ulcer at this time involved the leg

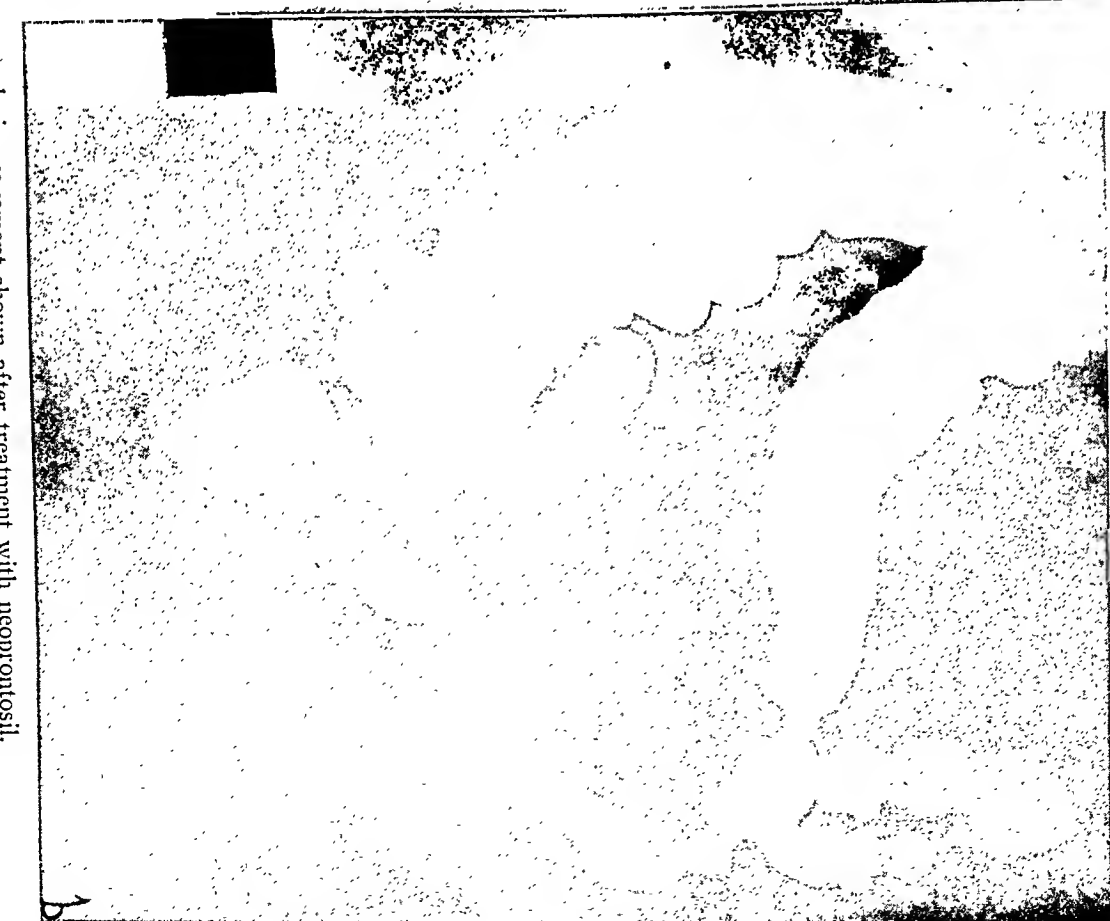
ment was carried out provided that active destruction of the bowel was not too great. For example, there were 11 patients who had involvement of the entire colon, grade 4, and in this group there were 10 cases in which the activity was of grade 2. Case 3 illustrated in figure 1 shows the improvement manifested roentgenographically in the large intestine following the use of neoprontosil. In two of these cases the disease, symptomatically and objectively, was inactive at the time of the last examination. In three others the disease was inactive symptomatically and in five, definitely improved. The one patient in this group whose condition did not improve was the patient previously cited whose treatment has thus far been too inadequate to arrive at a satisfactory evaluation. Involvement of the colon, grade 3, did not occur in any patients of group A, but there were two patients who had involvement as far as the splenic flexure, grade 2. The activity of the disease in these cases was graded 3 and 2; the final results showed the disease to be symptomatically inactive in one instance and improved in the other. Objectively both showed only minimal activity.

In the group of sixteen patients in which the disease was limited to the rectum and sigmoid, grade 1, and in which the activity of the disease was graded 1 to 2, in three the disease was symptomatically and objectively inactive at the time of the final examination. In five others the disease was symptomatically inactive; in six cases improvement had occurred and in two previously mentioned, treatment was a failure. Although not shown on the chart, it is further interesting to note that among those individuals in this group whose stools were very bloody and were increased in number, four to 15 daily, both the quantity of blood and the number of stools were in most instances greatly decreased on the third to the fifth day of treatment. In other words, blood disappeared from the stools of these individuals long before healing of a severely denuded bowel would have seemed possible. It is also interesting that the appearance of the mucous membrane proctoscopically in a number of cases was reported greatly improved and in some instances was even normal as early as two or four weeks after the beginning of treatment.

Of special interest in this series of cases are two in which there occurred the unusual complication of pyoderma gangraenosum, an ulcerated condition found in association with chronic ulcerative colitis and which has been described by O'Leary, Brunsting⁴ and one of us (Bargen²). In case 17, the ulcer which involved the right leg between the knee and ankle had begun to develop six weeks prior to admission to the clinic, at the time of an exacerbation of the colitis. Organisms were not recovered from it on culture. After 15 days of treatment with neoprontosil remarkable healing of the ulcer occurred. Symptomatic and objective improvement of the ulcerative colitis also took place. After this patient's return home, treatment with neoprontosil was temporarily abandoned due to difficulty in obtaining the drug. When the patient was last heard from the ulcer was incompletely healed but had shown no advancement (figure 2). The second



a



b

Two types of results appear in that group of results classified as excellent. The first type is that in which the disease at this time of evaluation was considered symptomatically (clinically) and objectively (proctoscopically) inactive. There were five such patients (cases 4, 7, 18, 21, 25). The second type of excellent result was in that group in which the disease was symptomatically inactive, of which there were eight patients (cases 3, 9, 12, 14, 19, 24, 26, 28). Six of these patients (cases 3, 9, 12, 24, 26, 28) had a final proctoscopic examination which showed that the activity of the disease was minimal. One patient (case 19) is included in this group because he did not have a final proctoscopic examination. One patient (case 4) had objective evidence of inactivity for several months; the disease became active, grade 2, during an acute respiratory infection and at the time of the last examination was symptomatically inactive although objectively (proctoscopically) the activity was graded 1.

The group in which fair results occurred includes those patients in whom definite improvement followed treatment, yet the final result was not good enough to be interpreted as complete inactivity of the disease. However, seven (cases 2, 5, 6, 13, 16, 17, 20) of the thirteen patients (cases 1, 2, 5, 6, 8, 10, 13, 16, 17, 20, 22, 23, 29) who appear in this group had a final proctoscopic examination which revealed minimal activity of the disease. In case 22, proctoscopic reexamination showed activity, grade 2; in two others (cases 1 and 8), there was activity, grade 1 and in three others (cases 10, 23, 29) a final proctoscopic examination was not made.

The third group of results which were classified as poor in which three cases appear deserve further mention. In case 27, the patient was an elderly woman; the disease which was limited to the rectum and sigmoid, was classified as grade 1. Initial response of the disease to the drug was favorable but treatment was abandoned after the patient returned home because of difficulty of obtaining the drug at a time when it was not yet on the market. The amount of the drug given, therefore, was inadequate.

In case 11 of this group, the disease involved the entire colon but was graded 1 although the symptoms had been comparatively constant. Up to this time, this patient has been under observation for only two months and has received but two courses of treatment of 14 days each. The duration of treatment thus far must be considered inadequate but it is questionable whether much can be accomplished for a condition of this type with extensive changes in the bowel owing to persistent chronic diseases.

The third patient (case 15) failed to show a satisfactory response after six weeks of treatment at the clinic, although there was a slight suggestion of improvement in the mucosa of the bowel. An adequate explanation cannot be offered for this failure. Experience with chronic ulcerative colitis has shown an occasional case similar to this which is refractory to any form of therapy.

It is notable that in this series of cases the amount of bowel involved did not seem to affect materially the final clinical result when adequate treat-

cavity contained about 15 c.c. of straw colored fluid. The right pleural cavity contained 200 c.c. of similar fluid, and the left 50 c.c. There were 300 c.c. of clear, yellow fluid in the pericardial cavity. There was no evidence of pleuritis or pericarditis. The heart weighed 530 grams. Numerous petechiae were noted in the visceral pericardium. The left ventricle was moderately hypertrophied and the right ventricle dilated. The mitral and pulmonary valves appeared normal. A large vegetative lesion was present on the aortic valve (figure 1). The right and posterior aortic cusps were covered by a large mass of soft friable vegetations about 2 cm. in diameter and 1 cm. in thickness. The adjacent portions of the right and posterior aortic cusps, and the aortic ring between them was eroded in such a manner that at this point there was an almost spherical outpouching or herniation 1.5 cm. in diameter. The first portion of the right coronary artery was encroached upon by this herniation. The bottom of this pocket was made up of the herniated aortic ring or upper portion of the interventricular septum, and the pocket invaded the right ventricle underneath the posterior portion of the medial cusp of the tricuspid valve. This valve leaflet was adherent to the herniation but not otherwise involved. The left and right aortic cusps were fused for a distance of about 8 mm. The root of the aorta and the coronary arteries were not sclerosed.

The right lung weighed 650 grams, and the left 615 grams. Cut sections of both lungs were of a uniform, rusty brown color, and somewhat doughy in consistency. There was evidence of slight edema, but no consolidation. The spleen weighed 1100 grams. On section it was of uniform red color and of soft consistency. There were no infarcts. The liver weighed 3900 grams. The surface was smooth. Cut section revealed it to be soft, pale, swollen, with a marked nutmeg appearance. The gastrointestinal tract was normal except for some congestion of the mucosa. The pancreas and adrenals appeared normal. The right kidney weighed 290 grams, and the left 310 grams. The surfaces were smooth. On section, they were swollen, congested, and cloudy. There were a few petechiae in the pelves. Permission was not obtained for examination of the brain.

Microscopic examination of the organs showed none of the tubercle-like epithelioid cell structures which have been described in many cases of brucellosis. The heart showed a focal myocarditis of moderate intensity. The cellular accumulations were small and composed mainly of small mononuclear cells. A section of the left aortic cusp not involved by the vegetations showed no definite evidence of an older inflammatory process, but there was a slight acute inflammatory reaction just under the surface. The right and posterior aortic cusps where they were involved by vegetations revealed a marked destruction of the valve tissue by a chronic inflammatory process. The vegetations consisted mainly of platelets and fibrin with a thin zone of lymphocytes at the periphery. There was much calcification present. There were large clumps of small coccoid organisms throughout the vegetations. The masses of bacteria in the vegetations appeared blue when stained by the Gram-Weigert method, even though brucella are gram negative organisms. This discrepancy will be commented upon shortly. The lungs presented the picture of atelectasis, emphysema, and chronic congestion. The liver sections showed moderate central necrosis, and the changes of passive congestion. The spleen showed no fibrosis but there was a cellular infiltration consisting of numerous macrophages, and small numbers of plasma cells and polymorphonuclear leukocytes in the pulp. The glomeruli of the kidneys exhibited a slight degree of endothelial proliferation. There were small foci of chronic inflammatory exudate throughout the interstitial tissue. In the periaortic lymph nodes there was a marked degree of hyperplasia of the sinus reticulum with beginning fibrosis. The sinuses contained numerous macrophages, and a finely granular brown pigment was noted in the reticular cells.

Postmortem Bacteriological Studies. Microscopic examination of a smear of the vegetation on the aortic valve stained by Gram's method revealed myriads of small,

cocco-bacillary, gram negative organisms having the morphological appearance of brucella. No other organisms were present. Material was cultured in liver-infusion broth from the aortic vegetation, kidney, spleen, heart's blood, lung, periaortic lymph node, pericardial fluid, bone marrow and liver. Pure cultures of *Brucella melitensis* var. *abortus* were obtained in this manner from the vegetation, kidney, spleen, heart's blood, and lung. Growth took place only in a jar having an increased carbon dioxide tension. The isolated organisms were agglutinated by brucella antiserum of the abortus type in a dilution of 1 to 2,560. Guinea pigs were inoculated with the cultures obtained from the heart's blood. When autopsied four weeks later, *Brucella melitensis* var. *abortus* was identified in pure culture from the animals' spleen.*

The anatomical diagnoses were: Brucella endocarditis with bacteremia; chronic splenitis; chronic congestion of the lungs and liver; focal myocarditis; chronic lymphadenitis.

DISCUSSION

There are several features of this patient's illness that merit further discussion. To recapitulate, he had a sudden departure from health with weakness, fever, and loss of weight as the outstanding symptoms. In addition, he developed chills and episodes of profuse perspiration. Agglutinins were present in the blood in a high titer for brucella organisms. No cardiac abnormality was found when he first consulted a physician. The signs of a progressive valvulitis appeared, and death was due to cardiac insufficiency. The chronological development of these signs and symptoms, with sufficient laboratory data, warranted a diagnosis of chronic brucellosis, and acute endocarditis. The appearance of embolic phenomena in the form of petechiae suggested a bacteremia, and the presence of a bacterial endocarditis.

It is significant that repeated blood cultures remained sterile. Huddleson¹⁰ has emphasized the difficulties encountered in culturing brucella from the blood. Special media must be employed, and brucella of the abortus variety appear to grow only in an atmosphere of increased carbon dioxide tension. We utilized Huddleson's technic and yet were unsuccessful in isolating organisms. The injection of the patient's blood into animals yielded negative results. That the patient had a bacteremia at some time is proved by the recovery of brucella from various organs at autopsy. Keefer¹¹ has recently called attention to those cases of bacterial endocarditis without bacteremia. He points out, with sufficient immunological data, that the blood may be rendered free of bacteria because of a high degree of immunity that develops, and that the bacteria are localized on the heart valves. However, embolic phenomena indicate bacteria are present in the blood at times. In the present case, immune bodies in considerable quantity were present in the blood as shown by the high agglutinin titer (1:5,120).

The skin test has been considered a useful adjunct by Huddleson¹⁰ and others¹² in the diagnosis of brucellosis. The usual procedure is to inject killed brucella organisms intradermally, and note any reaction 48 hours later at the site of the injection. A positive test consists of edema, redness and perhaps some pain over this area. We have used the skin test as an aid in the diagnosis of this disease, and reactions have been obtained in all patients with active

* We are indebted to Dr. O. McDaniel, Director of the Minnesota Department of Health, Division of Preventable Diseases, for coöperating with us in the study of this patient, and to Dr. L. S. Heathman and Miss M. MacLanahan for assistance in the isolation and identification of the organism.

brucellosis, except in the present case. Although several skin tests were done on the patient, at no time was there a positive reaction. It is of interest that although his blood agglutinated a suspension of brucella organisms in a titer of 1:5,120, when the same suspension in varying dilutions was injected into his skin, there was no reaction noted. It has been observed^{11, 13, 14, 15} that negative skin reactions occur in patients with subacute bacterial endocarditis due to streptococci of the viridans type when the filtrates of protein extracts of streptococci are injected intradermally. This absence of skin activity may be a useful aid in the diagnosis of obscure cases of subacute bacterial endocarditis.

We should like to point out the inadvisability of using the Gram-Weigert stain in differentiating gram negative and gram positive organisms in tissue preparations. We utilized this technic in studying sections of the vegetations from the aortic valve, and the organisms were stained a deep blue color. The organisms appeared to have the same morphological characteristics as *Streptococcus viridans*. Thus the histological appearance was the same as that seen in vegetative endocarditis due to the *Streptococcus viridans*. Smears from the vegetation stained by Gram's method showed gram negative cocco-bacilli. It was only by obtaining brucella organisms in pure culture from the vegetation that the true nature of the lesion was ascertained. Others^{16, 17, 18} have pointed out the discrepancies that result in the use of the Gram-Weigert stain, and have proposed more exact methods of study.

It is of interest that in the case cited a brucella infection was apparently superimposed upon a previously normal aortic valve. No cardiac murmurs were heard when the patient first became ill. Histological examination of that part of the valve not involved by vegetation, did not give evidence of an underlying chronic valvulitis. In subacute bacterial endocarditis it is not unusual for bacteria to localize on previously normal valves.¹¹

SUMMARY AND CONCLUSIONS

1. Brucella endocarditis is an infrequent complication arising in patients with brucellosis. It may be caused by any one of the three varieties of *Brucella melitensis*.

2. The literature is reviewed, and the clinical and pathological findings of a fatal case of brucella endocarditis due to brucella of the abortus variety are presented and discussed.

BIBLIOGRAPHY

1. ALBERTINI, A. V., and LIEBERHERR, W.: Beiträge zur pathologischen Anatomie der Febris Undulans Bang, Frankfurter Ztschr. f. Path., 1937, li, 69.
2. SCOTT, R. W., and SAPHIR, O.: *Brucella melitensis* (abortus) bacteremia associated with endocarditis, Am. Jr. Med. Sci., 1938, clxxv, 66.
3. CASANOVA, F., and D'IGNAZIO, C.: Endocardite Vegetante Aortica da brucella melitense, Minerva med., 1933, ii, 209.
4. ROTHMAN, A.: Bangsche Erkrankung mit ulzeröser Endocarditis, Verhandl. d. deutsch. path. Gesellsch., 1935, xxviii, 194.
5. DE LA CHAPELLE, C. E.: Vegetative endocarditis due to the *Brucella melitensis* with a case report, Am. Heart Jr., 1928-29, iv, 732.
6. LEVY, D. F., and SINGERMAN, B.: *Brucella melitensis* bacteremia associated with vegetative endocarditis, Am. Heart Jr., 1938, xv, 109.

7. HARDY, A. V., JORDAN, C. F., BARTS, I. H., and HARDY, G. C.: Undulant fever: with special reference to a study of brucella infection in Iowa, Nat. Inst. of Health Bull., No. 158, Dec. 1930, Washington, D. C.
8. GOUNELLA, H., and WARTER, J.: Endocardite ulcero-vegetante au cours d'une melito coccie, Bull. et mém. Soc. med. d. hôp. de Par., 1935, li, 1197.
9. RENNIE, J. K., and YOUNG, C. J.: Malignant endocarditis due to *Brucella abortus*, Brit. Med. Jr., 1936, i, 412.
10. HUDDLESON, I. F.: Brucella infections in animals and man, 1934, Commonwealth Fund, New York City.
11. KEEFER, C. S.: Subacute bacterial endocarditis: active cases without bacteremia, ANN. INT. MED., 1937, xi, 714.
12. KELLER, A. E., PHARRIS, C., and GAUB, W. H.: Diagnosis of undulant fever: the opsonocytaphagic, allergic and agglutination reactions, Jr. Am. Med. Assoc., 1936, cvii, 1369.
13. HOWELS, K. M., and CORRIGAN, M.: Skin reactions with bacterial filtrates of anhemolytic streptococcus, hemolytic streptococcus, and *B. typhosus*, Jr. Infect. Dis., 1928, xlii, 149.
14. DERRICK, C., and FULTON, M.: Skin reactions in patients and normal individuals to protein extracts of streptococci, Jr. Clin. Invest., 1931, x, 121.
15. LEVINE, S. A.: Clinical heart disease, 1936, W. B. Saunders Co., Philadelphia, p. 194.
16. MACCALLUM, W. G.: A stain for influenza bacilli in tissues: a combination of Good-pasture's and Weigert's stains, Jr. Am. Med. Assoc., 1919, lxxii, 193.
17. BROWN, J. H., and BRENN, L.: A method for the differential staining of gram-positive and gram-negative bacteria in tissue sections, Bull. Johns Hopkins Hosp., 1931, xlviii, 69.
18. RUDNIKOFF, I., and STAWSKY, H.: Modified method for staining gram-positive and gram-negative organisms in tissue sections, Arch. Path., 1935, xix, 543.

BERI-BERI; SEVERE MANIFESTATIONS OF BOTH THE 'WET' AND 'DRY' FORMS IN THE SAME PATIENT; RECOVERY FOLLOWING TREATMENT*

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THE cardiovascular complications of inadequate vitamin consumption have been traced to vitamin B₁ deficiency. The specificity and cure of the cardiac manifestations of this avitaminosis recently were reaffirmed by Hashimoto,¹ who reported a case in which dramatic recovery followed the intravenous administration of minute quantities of purified and concentrated vitamin B₁.

The condition may manifest itself in a 'dry' type, characterized by muscle wasting and peripheral neuritis, or a 'wet' type in which generalized edema and cardiovascular disturbances predominate. The combination of an acute form of one type with a mild form of the other is uncommon, and likewise the presence of a severe form of both types in the same individual is rare.²

A low standard of living, derangements of pregnancy resulting in poor food intake or utilization and chronic alcoholism are instances in which the outstanding factor is the inability or reluctance of the patient to obtain or to utilize a diet adequate in vitamin requirements.

* Received for publication August 3, 1938.

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We are reporting a case in which all the signs and symptoms of both the 'wet' and 'dry' forms of B₁ avitaminosis appeared after a young asthmatic woman, allergic to many foods, curtailed her diet drastically in an effort to obtain relief.

CASE REPORT

B. N., a 25 year old factory worker, first developed sinusitis at the age of 14. Asthmatic symptoms which were relieved by adrenalin appeared one year later. At the age of 18 she was confined to bed for eight weeks because of bronchopneumonia. The symptoms of sinusitis and asthma became more severe, failing to respond to sinus irrigations, removal of nasal polyps and other measures.

The patient was given cutaneous tests and found sensitive to rye, tomato, barley, cheese, cauliflower, all grain cereals, fish, coffee and banana. Elimination of all possible offending substances to the point of starvation failed to ameliorate her asthmatic seizures.

During January 1936, a course of injections of autogenous vaccine was started. Following the first injection, she complained of nausea, vomiting and exacerbation of her asthmatic symptoms, and the series was discontinued.

Diarrhea lasting five days followed. Neither blood nor mucus was present in her stool. The gastrointestinal discomfort was continuous until April 1936, at which time she became bedridden. Asthenia and anorexia became progressively worse. During this entire time she continued to restrict her diet rigidly. Nevertheless, the asthmatic seizures became more frequent.

During June 1936, she noted pain, weakness and stiffness of both hands and feet. The pain, which initially was worse at night, soon became almost continuous. Paresthesias appeared in both the upper and lower extremities.

Pitting edema of the lower and upper extremities then was noted. Radiographic examination of the chest on June 11, 1936, was negative. Another roentgenogram of the chest taken on July 23, 1936, revealed the presence of bilateral hydrothorax and an increase in the frontal silhouette of the heart. Physical examination of the heart at that time gave no positive diagnostic findings. There were no subjective symptoms which might have been attributed to circulatory failure.

Several leukocyte counts during June and July 1936, showed a leukocytosis varying from 10,000 to 30,000, with an eosinophilia varying from 30 per cent to 70 per cent.

A biopsy taken from the deltoid muscle revealed no evidence of trichinosis. The vascular structures were normal. Repeated examinations of the urine proved negative.

The patient was seen again in March 1937. At that time there was pronounced shortness of breath. The burning and tingling sensations in her extremities had become constant, and were extremely painful. Small black spots had appeared on the toes of both feet and the distal phalanges of both hands during February 1937. Within a month they coalesced and developed into dry gangrene (figure 1a). Oscillometric readings made on March 17, 1937, showed marked diminution in the circulatory beds of all four extremities.

On March 4, 1937, pretibial edema reappeared. Radiographic examination of the chest revealed fluid in both pleural cavities and an increase in the size of the heart shadow. An electrocardiogram taken on April 1, 1937, revealed regular sinus rhythm. The ventricular rate was 110. The 'S'-wave in Lead I was prominent. There was a tendency towards right axis deviation. The p-R interval was 0.18 second.

The degree of the edema progressed rapidly, so that by the end of April 1937, anasarca was present. The serum albumin was 2.1 per cent, serum globulin 2.6 per cent. She was given several mercurial diuretic injections which resulted in excellent

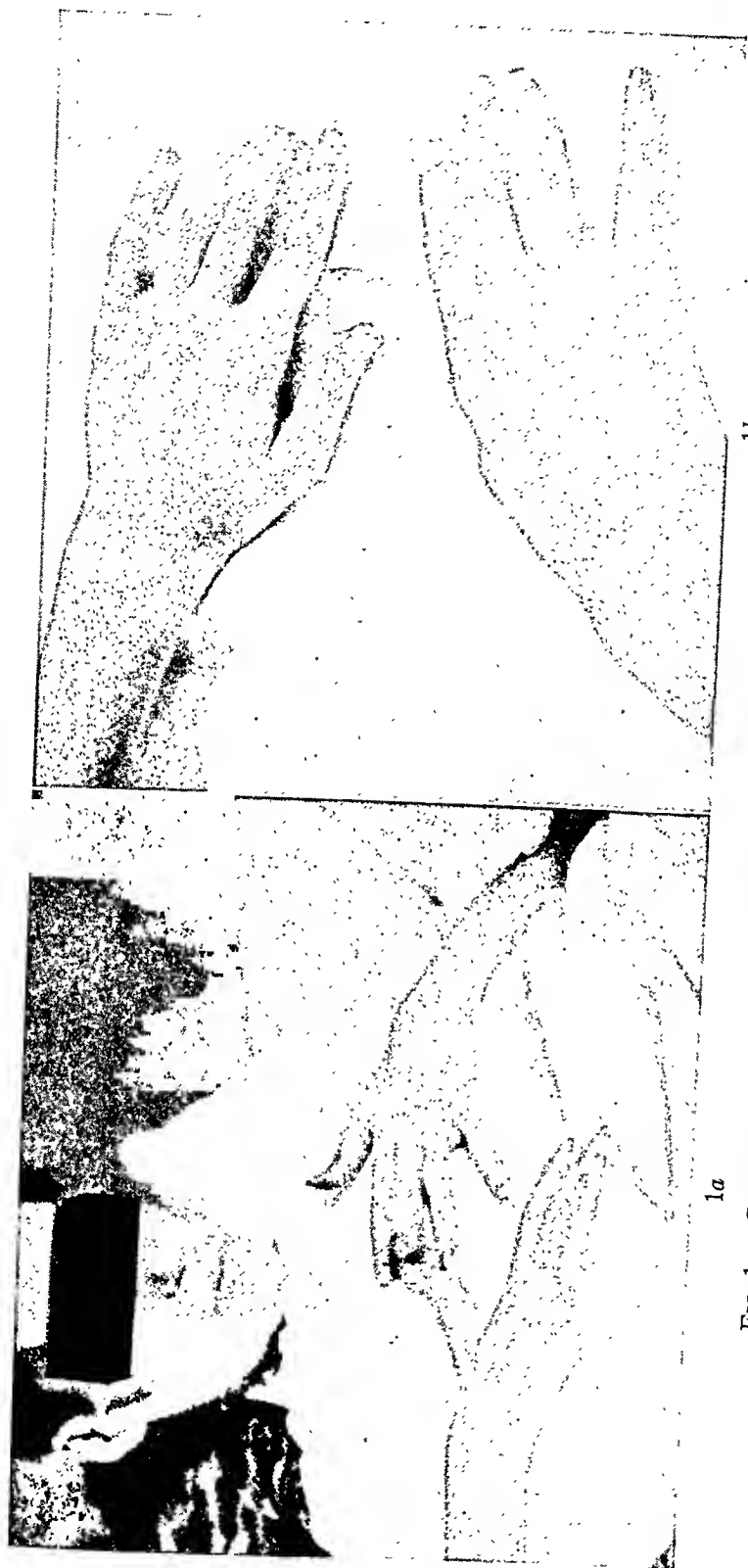
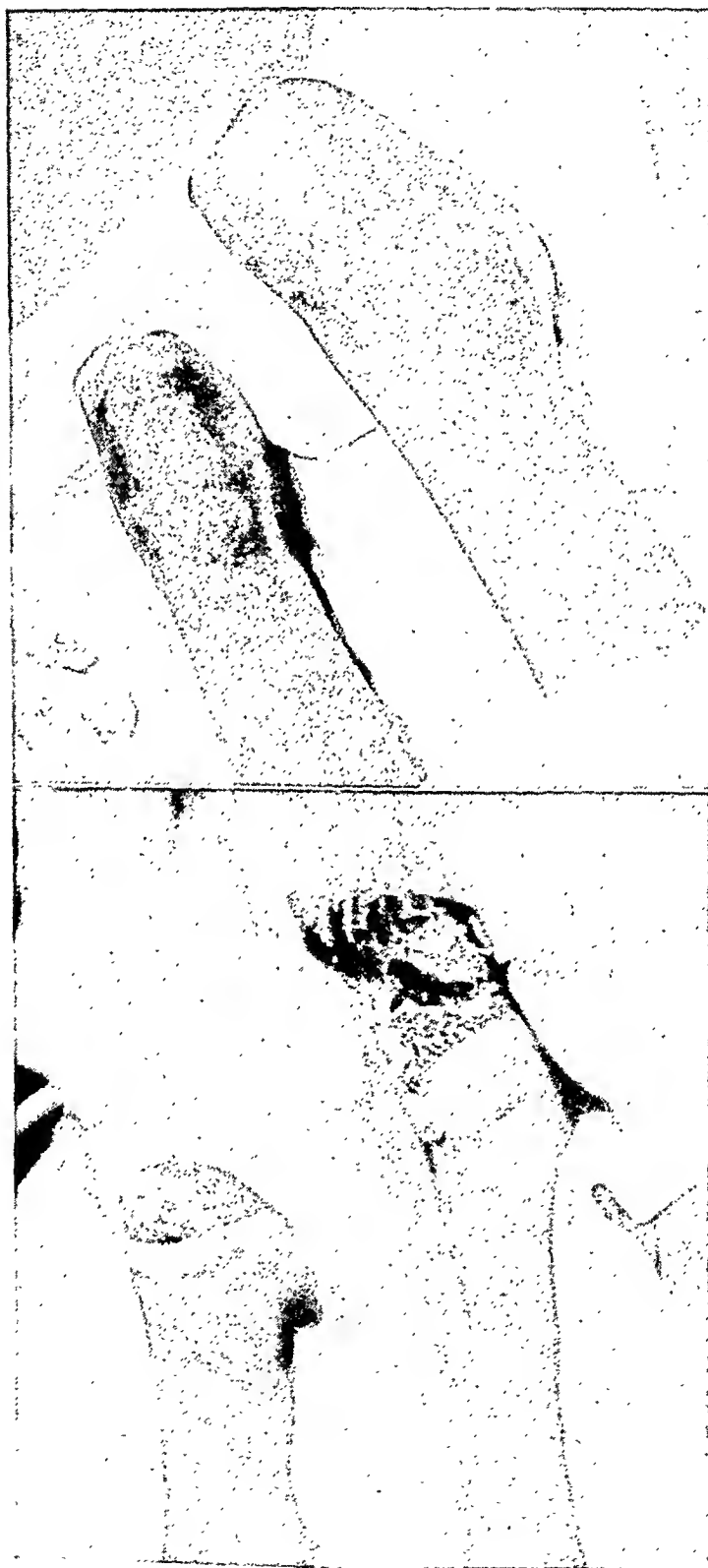


FIG. 1a. Gangrene of finger tips before vitamin therapy.
FIG. 1b. The gangrene of the finger tips has healed almost completely, after vitamin therapy.



2a

2b

FIG. 2a. Spontaneous amputation of the left foot, unhealed. Gangrene of distal half of the right foot.
FIG. 2b. After surgical revision of right foot and vitamin therapy.

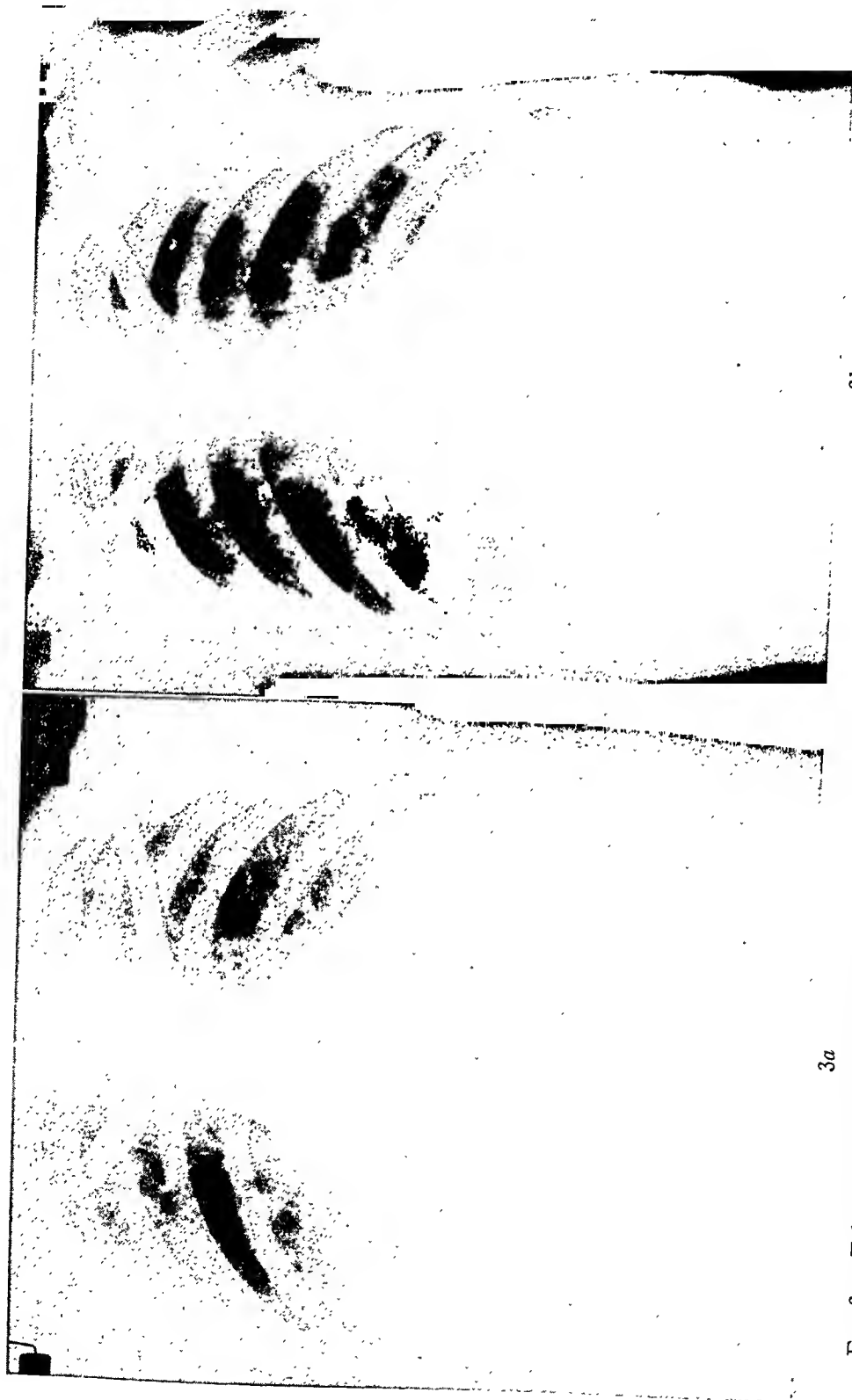


FIG. 3a. Teleoroentgenogram taken May 17, 1937, showing bilateral hydrothorax and increase in the size of the heart shadow.
FIG. 3b. Teleoroentgenogram taken June 12, 1937, following mercurial diuretics and an adequate diet. The lung shadows are clearer, but some fluid persists in the costophrenic sinuses. The heart shadow is smaller.

diuresis but in little decrease of the edema. Dyspnea, however, became less pronounced, and the patient was somewhat more comfortable.

On April 26, 1937, a spontaneous amputation of the distal third of the left foot occurred while the patient was in bed (figure 2a). The tissue proximal to the site of amputation showed evidences of satisfactory circulation. Examination of the specimen revealed nothing of diagnostic value.

She remained alert and coöperative, but still refused food. On physical examination during May 1937, the deep and superficial reflexes were found equal and active. No pathologic reflexes could be elicited. The heart rate was 80 per minute. The heart sounds were of poor quality, and no murmurs were audible. There were signs of fluid in both pleural cavities, confirmed by radiographic examination (figure 4a). Pitting edema up to the waist was so pronounced that a definite line of demarcation could be seen separating the edematous lower half of her body from the wasted upper half. Her blood pressure was 140 mm. of mercury systolic and 100 mm. diastolic.

Both upper extremities were markedly atrophied, cold and cyanotic. The terminal phalanges of both hands and the distal phalanges of the right foot were shrivelled and black, presenting the picture of dry gangrene. Necrotic bone protruded from the site of the spontaneous amputation. A surgical revision of the amputation stump of the left foot and amputation of the toes of the right foot were performed.

Histologic examination of tissue taken from the left gastrocnemius muscle at this time revealed normal vascular structures. Blood counts showed a leukocytosis varying from 11,500 to 18,000. The highest eosinophile count was 8 per cent. On several occasions no eosinophiles could be seen in the blood smears.

The serum proteins remained low, the albumin being 2.1 per cent and the globulin 2.6 per cent. Her weight was 86 pounds, a loss of 40 pounds since the onset of her illness.

Examinations of the urine showed the presence of albumin varying in amount from one to four plus. The blood urea nitrogen never exceeded 25 mg. per cent. The blood chlorides were 450 mg. per cent, and the cholesterol was 160 mg. per cent. The basal metabolic rate was minus 11.

Repeated mercurial diuretics administered intravenously and by rectal suppositories were very effective.

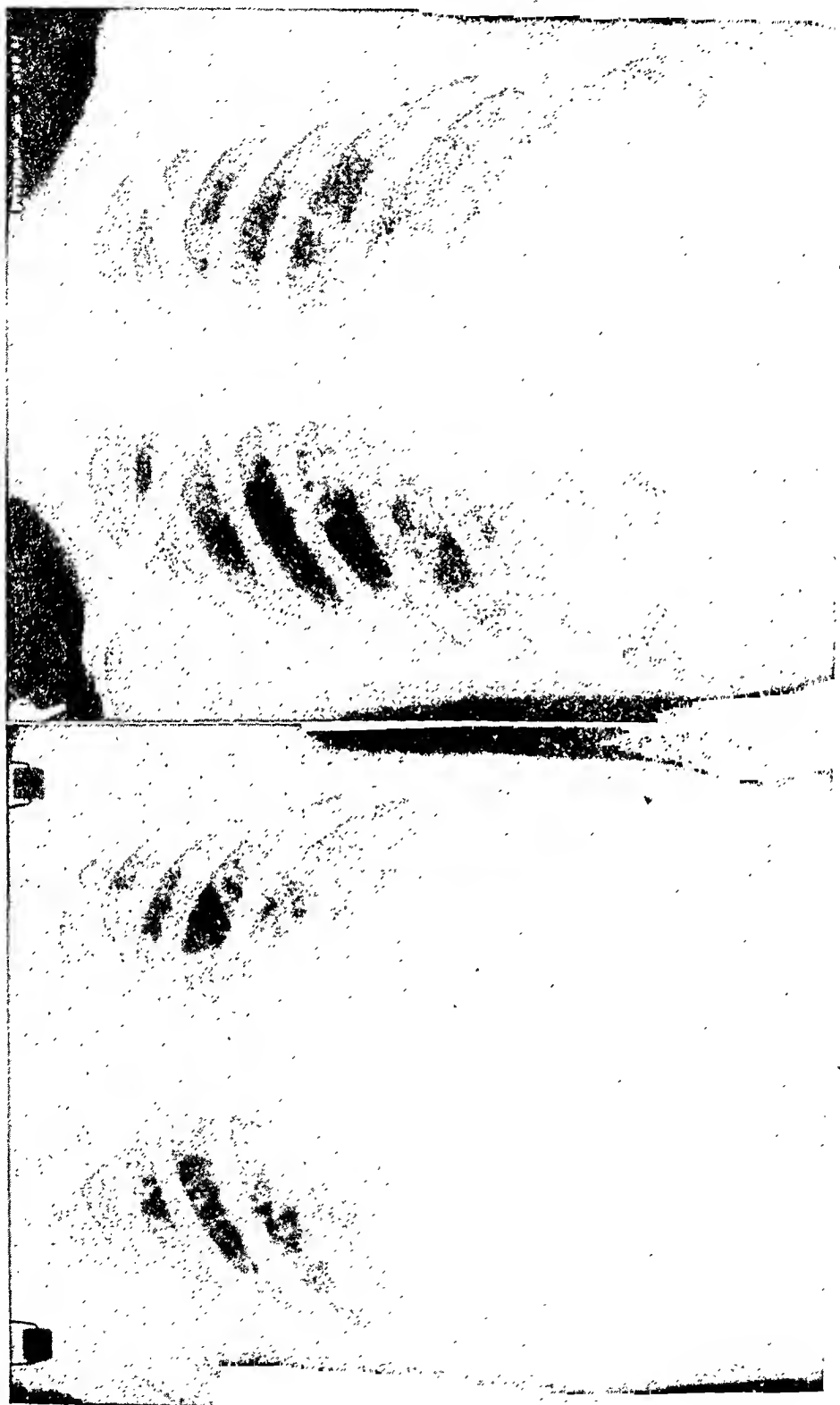
During the latter part of May 1937, the patient was encouraged to increase her diet, which was fortified with capsules of vitamin B concentrate.* At first she was recalcitrant, but after a few days of encouragement she began to take a fairly ample diet.

Improvement followed rapidly. The mercurial diuretics became even more effective than heretofore. Radiographic examination of the chest on June 12, 1937, showed the pleural cavities to be practically free from fluid (figure 4b).

During the next month difficulty again was encountered because she refused both her food and medication. A chest radiogram taken on July 23, 1937, showed reaccumulation of fluid in both pleural cavities (figure 4a). Further mercurial diuretics together with an increased diet and vitamin concentrates taken regularly again resulted in definite, and this time, lasting improvement. The chest fluid and peripheral edema vanished, and neither has recurred since.

During the next four months the patient made continual progress. The signs and symptoms of cardiovascular insufficiency disappeared, and the cardiac silhouette reassumed a normal configuration (figure 4b).

* The vitamin was first administered in the form of capsules containing vitamins A, B and D. Tablets of thiamin chloride, containing 1 mg. of thiamin chloride were added after the first week. The average daily dose during the first six weeks of treatment was equivalent to eight to ten milligrams of thiamin chloride daily in addition to a diet planned to contain a high amount of natural vitamin B.



4a

4b

FIG. 4a. Teleoroentgenogram taken July 23, 1937. The pleural effusion has recurred after the patient refused her diet.
FIG. 4b. Teleoroentgenogram taken September 3, 1937, after the patient had been on an ample diet fortified with vitamin B-1. The lung fields are clear, and the heart shadow is smaller. Some residual infiltration is seen at the right base.

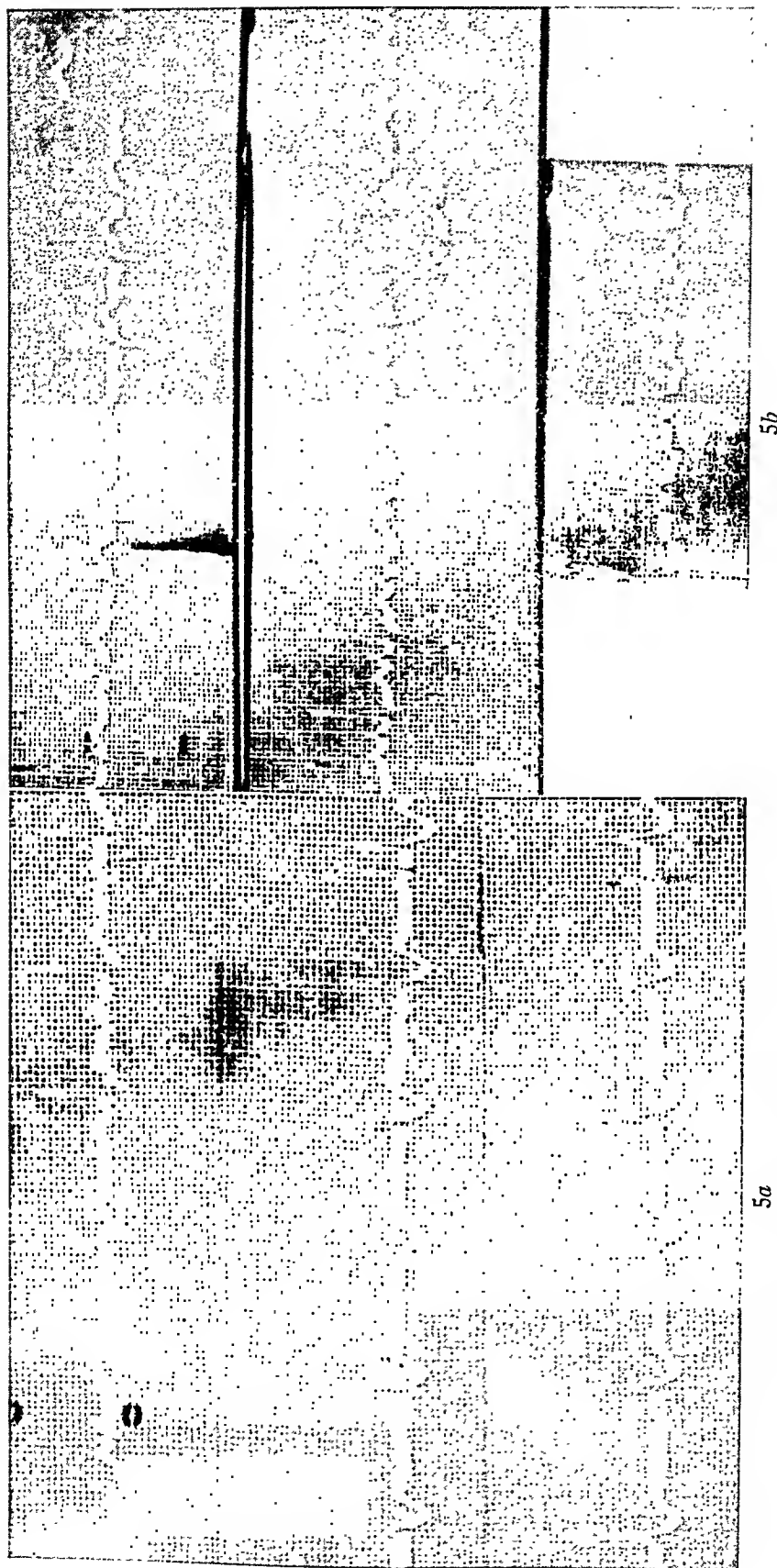


FIG. 5a. Electrocardiogram taken October 3, 1937. Note inversion of the "T"-waves in Leads II and III.
FIG. 5b. Electrocardiogram taken June 2, 1938. The "T"-waves in Leads I and II are erect. An occasional auricular extrasystole is present in Lead I.

An electrocardiogram (figure 5a) taken on October 3, 1937, showed regular sinus rhythm. The P-R interval was 0.24 second. The T-waves in Leads II and III were inverted, and the R-T take-off was abrupt and low. A subsequent electrocardiogram taken on June 2, 1938 (figure 5b) showed occasional auricular extrasystoles. The P-R interval was 0.18 second. The T-waves in Leads I and II were erect, and inverted in Lead III. The R-T take-off was normal.

The painful sensations in the extremities gradually diminished, and the gangrenous finger tips began to show signs of renewed vitality. At present there is definite wasting of the soft tissues of the ungual extremities of both hands and loss of finger tactile sensibilities (figures 1b). The stumps of both feet have a definitely pink, healthy appearance, and are not painful (figure 2b). All four extremities have recovered their normal contour and texture.

Asthmatic symptoms still are present, but are controlled more easily with adrenalin. The patient is cheerful, and partakes in occupational therapy work. She has gained considerable weight.

COMMENT

This patient is one in whom the manifestations of both the "dry" and "wet" forms of beri-beri appeared at about the same time, and over the period of a year advanced to unusually severe forms. The prolonged clinical course and the apparent cure may be taken as an indication that even far-advanced cases may respond well to treatment.

The relationship between the dietary restrictions and ensuing avitaminosis is apparent. It seems that severe elimination diets because of food sensitivities may be added to the list of possible causes of hypovitaminosis.

The gangrene of the fingers and toes progressing as far as spontaneous amputation is unusual. The small black spots which appeared first on the fingertips and toes in all probability were foci of local gangrene. In spite of the negative findings in the blood vessels of the muscle biopsied the presence of a generalized vascular abnormality of a spastic nature must be postulated. This is borne out by the oscillometric readings made during the height of the disease, and the return of normal color and moisture of the extremities after therapy had been instituted.

Cardio-respiratory symptoms did not appear until the patient had been ill for nine months. Hydrothorax and pericardial effusion, however, had been present from the third month of her illness. Mercurial diuretics were effective during the period of avitaminosis, but their potency was augmented considerably by adequate diet and vitamin concentrates. The reversibility of the electrocardiographic and radiographic findings is worthy of mention.

The tremendous edema no doubt had a nutritional as well as an avitaminotic factor. Repeated examinations of the blood serum proteins showed hypoproteinemia during the course of the disease, with a prompt rise after therapy had been administered.

Exercise as a factor in the development of heart failure is ruled out inasmuch as the patient was bedridden before the subjective symptoms of heart failure appeared.

The marked eosinophilia noted during June and July 1936 probably was on an allergic basis rather than related to the avitaminosis. The eosinophilia disappeared later, while the manifestations of beri-beri continued.

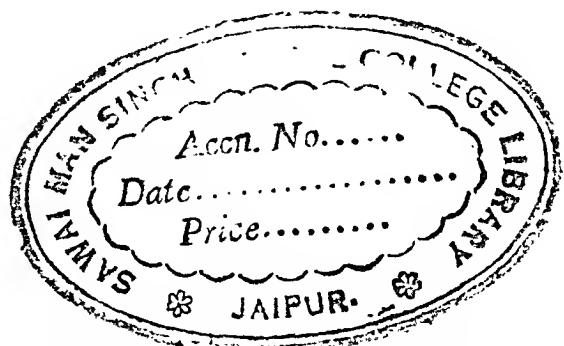
SUMMARY

An asthmatic patient is reported, in whom severe manifestations of both the "wet" and "dry" forms of beri-beri appeared after restriction of diet.

Recovery followed increase in diet and addition of vitamin B concentrates.

REFERENCES

1. HASHIMOTO, H.: Acute pernicious form of beri-beri and its treatment by intravenous administration of vitamin B-1, *Am. Heart Jr.*, 1937, xiii, 580-588.
2. WEISS, S., and WILKINS, R. W.: Disturbances of the cardiovascular system in nutritional deficiency, *Jr. Am. Med. Assoc.*, 1937, cix, 786-793.



EDITORIALS

SMALLPOX

Public Health Reports ¹ draws our attention to the astonishing prevalence of smallpox in the United States. In 1937 this country led all other nations of the world, except India, in the number of smallpox cases reported. The number occurring in the United States that year was 11,673. In 1938 an increase was noted to approximately 15,000.

These figures are the more humiliating when we learn that in 1936 England and Wales, with a population of 40,839,000, reported only 12 cases; France, with 41,906,000 population, reported 273 cases; and Germany, with a population of 67,346,000, reported no cases.

The record of the various states as to smallpox incidence is very uneven. The mountain area of the west showed the highest incidence in 1938, 38.4 cases per 100,000 population. The west north-central and Pacific areas likewise showed incidences above 30 per 100,000. In the other central areas the incidence averaged close to 11 per 100,000. On the other hand the states along the Atlantic coast are practically free from smallpox. In 1938 the New England and middle Atlantic areas did not report a single case and in the south Atlantic area the incidence was 0.6 per 100,000.

Recently, in a Statistical Bulletin of the Metropolitan Life Insurance Company, it was stated that New Jersey, with a population of about 4,400,000, has not had a case of smallpox for more than seven years, while the states of North Dakota, South Dakota, Montana, Idaho, Oregon, Wyoming and Utah, with a combined population less than that of New Jersey, reported during the same period a total of more than 12,000 cases.

The eastern seaboard suffered such ravages from virulent smallpox in Colonial days and in the last century, and moreover had so many and such convincing demonstrations of the efficacy of vaccination, that compulsory vaccination is universally prescribed and well enforced. The same is not true in the afflicted area.

For the last 20 years, it is true, the type of smallpox seen has for the most part been mild with a very low mortality. Older physicians, however, well remember the day when the mortality in unprotected cases ranged between 25 and 35 per cent. That virulent forms can still occur was demonstrated in the Minneapolis epidemic in 1924 when 993 cases occurred with 221 deaths. There is no sound basis for a belief that smallpox will permanently retain its present mild form.

Should a virulent type of smallpox be imported or develop locally its ravages will be limited to the unprotected population. Those communities which allow a large part of their population to go unvaccinated will suffer severely. It is surely the continuing duty of all physicians to urge the passage of compulsory vaccination bills before such calamities have occurred.

¹ Why smallpox?, Public Health Rep., 1939, liv, 1091-1093.

THE SPREAD OF ROCKY MOUNTAIN SPOTTED FEVER

The gradual spread of Rocky Mountain Spotted Fever into new areas of the country is attracting the attention of both public health officials and of practising physicians. The number of cases is nowhere very great but the severity of the disease and its relatively high mortality in certain regions have given rise to a considerable degree of apprehension on the part of the public. The presence of ticks, known to be capable of transmitting the disease, in the underbrush of recreational areas has naturally led to some anxiety among those planning vacations. In foci where numerous cases have occurred depreciation in land values results.

The disease was first known to the medical profession as a highly fatal fever, accompanied by a generalized, often hemorrhagic, eruption, occurring in the western part of Montana and especially in the Bitter Root Valley. It is now known to be one of a world wide group of diseases due to the *rickett-siae*. The present conception is that it is primarily a disease of the native fauna and that it is carried from animal to animal by the bite of ticks and fortuitously from animal to man by the bite of such ticks as have the characteristic of feeding upon both the infected animal species and man. In addition the disease agent may survive for long periods in the body of the tick; it may be transmitted from tick to tick during copulation; and from the female tick through the egg to the larva.

Of the ticks which fasten readily upon man two have been proved to be of chief importance in carrying the disease: *Dermacentor andersoni* (the Rocky Mountain wood tick) whose range is roughly from the west-central states to the Pacific coast with maximum concentration in the Rocky Mountain region; and *Dermacentor variabilis* (the American dog tick) which is distributed generally, though in varying frequency, from the Atlantic coast to the Rocky Mountains.

Prior to 1930, reports of the disease were practically confined to states lying west of the east-central group but since that time an increasing number of cases has developed in the eastern half of the country. In this new area the greatest number of cases has been reported from the states of Maryland and Virginia and from the District of Columbia, and the fewest from the New England states. The relative scarcity of the *Dermacentor variabilis* in the New England group of states may explain the infrequency of the disease in this region.

The seasonal incidence of the disease corresponds both in the East and West with the seasonal period of activity of the two tick species chiefly involved in transmission. Since at this time the tick season for 1939 is practically over in both areas it is possible from the reported cases to form some estimate concerning the present relative frequency of Rocky Mountain Spotted Fever in different parts of the United States. In a recent number of Public Health Reports¹ the cases reported from February 26 to September 9,

¹ Prevalence of disease. United States: Rocky Mountain Spotted Fever, Public Health Reports, 1939, liv, 1699.

1939, are given by states. Cases have been reported from 25 states. The total is 485.

Of these reporting states 10 are eastern states, extending from New York to Georgia. The total of reported cases in this group of states is 218. The largest number of cases in any state was in Maryland where 66 cases were reported. This number incidentally was the highest for any state in the union.

From the central states cases have been reported from seven states totaling 99. Iowa reported the highest number, 27, for any state in this group.

Of the entire western group of states only eight reported cases, the total being 168. Wyoming reported the largest number of cases, 43. From Montana, the original home of the disease, only 22 cases were reported.

It is evident that not only has Rocky Mountain Spotted Fever greatly extended its range in the last decennium but that at the present time more cases are occurring in the eastern section of the country than in the Rocky Mountain region. Indeed, in Maryland, the District of Columbia, Virginia and North Carolina alone, a total of 160 cases was reported, which is very close to one-third of the total for the whole country.

Such an outcome was predicted when the disease was first recognized in the East, on the basis of the greater density of population in the eastern states and the apparent abundance both of susceptible fauna to serve as a reservoir and of ticks capable of transmitting the disease.

Our knowledge of the cycles of incidence of this disease and of all the factors involved in its perpetuation and transmission is as yet quite insufficient to warrant prediction as to the future part it may play as a public health problem. It is encouraging, meanwhile, to know that improvements in vaccine production for the rickettsial diseases are being rapidly attained.

REVIEWS

Handbook of Hematology. In 4 volumes. Edited by HAL DOWNEY, Professor of Anatomy, Medical School, University of Minnesota, Minneapolis. Thirty-seven contributors. 3136 pages. 1448 illustrations, including 50 colored plates. Paul B. Hoeber, Inc. (Medical Book Department of Harper Brothers), New York. 1938. Price, \$85.00 set. Volume two—pages 699–1586.

Volume two of the *Handbook of Hematology* presents, in nine sections, further discussions of some fundamental aspects of the morphology and physiology of the hematopoietic system. The topics included range from a presentation of data concerning blood studies in representative species of the animal kingdom, to a consideration of the work done with tissue cultures of blood cells and blood-forming organs. In all chapters the information is presented in scholarly fashion and is supplemented by a plentitude of illustrations which are excellent throughout.

Beginning with a section devoted to comparative hematology, there are succeeding chapters covering particular parts of the hematopoietic system. Thus, in separate sections are discussed the embryogenesis of mammalian blood, macrophages, fibroblasts, lymphatic tissue, the reticulo-endothelial system, and the von Kupffer cells of the liver. The discussion of these topics by individual contributors has resulted in a repetition of similar material in some places. In all sections the data appear to lend strong support to the monophyletic theory of blood cell origin. Jordan, in the section on comparative hematology, notes that even in the invertebrates the stem cell is a lymphocyte-like element of mesenchymal origin which has the general characteristics of the mammalian small lymphocyte. The inter-relationship of cells of the connective tissues with blood cells is noted in several sections. Fundamental questions as to the development potencies of these cells are discussed. The classical contributions of Maximow to this subject are frequently utilized in the four sections contributed by William Bloom. These data, although presented in a lucid, often brilliant manner, do not entirely clear the air of the various contradictory theories of blood-cell origin. The results of tissue cultures of these cells have as yet been of only minor significance. Many fundamental questions, including Maximow's observations on the transformation of lymphocytes into granulocytes, remain to be solved perhaps by the introduction of newer technical methods in this difficult field.

The largest section in this volume is that devoted to a detailed exposition of the reticulo-endothelial system. In aiming for completeness the author, R. H. Jaffe, has included many data which are probably more of historical interest than of practical value. There is, moreover, considerable space given to discussion of the part played by these cells in disease entities not directly of hematological interest. The wisdom of the inclusion of this material is somewhat doubtful.

Of more interest to the clinician is the section devoted to discussion of the normal blood values in infants and children and also that on monocytic leukemia. The former will undoubtedly serve as a constant source of reference for the pediatrician as well as the clinical hematologist. The chapter on monocytic leukemia is in reality a critique of all the available clinical material with reference to the existence of this entity as a distinct variety of leukosis. Downey is of the opinion that there exist two hematological varieties of monocytic leukemia which are designated respectively as the Schilling and Naegeli types. In the former, widespread proliferation of the R-E system is found at autopsy, whereas, in the latter, the formation of monocytes from myeloblasts can be observed. The former must be differentiated with care from those conditions known to produce systemic proliferation of the system of histocytes.

The accumulation of the material in this volume represents a task for the accomplishment of which the editor, publisher, and individual authors are due the appreciation of all interested in hematology.

M. S. S.

The Mechanism of Thought, Imagery, and Hallucination. By JOSHUA ROSETT, M.D. 289 pages; 26 × 18 cm. Columbia University Press, New York City. 1939. Price, \$3.00.

This book is an investigation into the neuro-physiological basis of the mechanism of thought, imagery, and hallucination. The style in which the book is written is unusually lucid and the clarity of exposition is not a little heightened by the frequent use of strikingly apt analogies and comparison.

The book is divided into two parts: one—fundamentals, and two—the mechanisms. Following an introduction that serves as a brief survey of the problem of consciousness as dealt with by philosophers, the author devotes a chapter to the description of Hughling Jackson's law of evolution and dissolution of the nervous system and its application to different phases of the conscious state. There are two important and exceedingly clear chapters on the physical basis of the emotions and on the autonomic nervous system and its relation with every bodily activity. The first portion of the book is closed by a chapter on representation and symbolism that is both informative and entertaining because of the use of a dry humor in the choice of illustrative examples. The second part of the book deals with the phenomena of thought, imagery, and hallucination and their mechanism as evidenced in the sequelae of injuries of the sensory receptive areas of the cerebrum, in the epileptic seizure, in the state of attention, and in sleep. Each chapter is followed by an excellent summary and well-selected references.

Psychological medicine has long been seeking for an adequate biological explanation of mental phenomena and Dr. Rosett has not only indicated the direction of further investigation but has made a definite contribution in this field. This is a stimulating and thought provoking book and should be of interest to physicians in general, as well as to neurologists and psychiatrists.

B. F. V.

The Emotional Factor in Visceral Disease. By H. G. MCGREGOR, M.D., M.R.C.P. 198 pages; 22.5 × 14 cm. Oxford University Press, London. Humphrey Milford. 1938. Price, \$3.00.

After a brief introduction by Dr. R. D. Gillespie, Dr. McGregor's book is divided into an excellent study of the various theories of emotion and its effect on physiologic function, followed by sections on the digestive system, respiratory system, cardiovascular system, and "the emotion-reaction mechanisms." In each of these sections the author reviews experimental work and what is known of normal changes in physiology both in man and animals under various emotional stresses; then takes up specific disorders. In the digestive system, for instance, he pays particular attention to peptic ulcer, ulcerative colitis, bloody diarrhea, and mucous colitis; in the respiratory system to asthma; in the cardiovascular system to "soldiers' heart" and blood pressure changes. All the way through he offers suggestive evidence that in many cases these disease pictures are primarily the result of emotional factors, illustrating these assertions with cases which are suggestive but by no means prove the point.

There is a rather misleading tendency at times to attribute specific pictures to specific cause. He suggests, for example, that gastric ulcer is the result of fear; colitis the result of immaturity; asthma the product of a certain type of personality. We doubt that any such specific constellations can be demonstrated and feel that many of the conclusions drawn are too far reaching.

The case histories are exceedingly brief. This may account for the fact that they seem rather misleading at times.

Throughout the book there are many excellent observations. The sections on the endocrines and the autonomic nervous system are stimulating. Treatment as suggested sometimes seems too simple and too satisfactory to be true, but ways are suggested in which every practitioner can be helpful to the type of patient who is apt to be passed over.

Dr. McGregor does not advocate protracted or extended methods and reminds us that deep and prolonged treatment is frequently unnecessary. The book is well written and very readable. Inasmuch as it presents a point of view too easily neglected, we feel that it is provocative enough to be an addition to one's library.

H. M. M.

Principles and Practice of Ophthalmic Surgery. By EDMUND B. SPAETH, M.D. 835 pages; 24 × 15.5 cm. Lea and Febiger, Philadelphia. 1939. Price, \$10.00.

The first chapter of this volume deals with anesthesia, preparation of patient, and instruments to be used. Following this are chapters on general pathology of the orbit, its surgical treatment, and plastic repair of deformities; surgery of the lacrymal apparatus; enucleation and allied operations; surgery of the ocular muscles, and its indications. There are two chapters on plastic surgery and five on surgical conditions of the lids. A chapter on the anatomical factors connected with surgical procedures on the eyeball precedes a description of the surgery of the conjunctiva, sclera, cornea and iris. General considerations connected with cataract surgery, the technic of cataract operations, indications and contra-indications for various procedures, and their complications are discussed in detail. Glaucoma and retinal detachment are as completely considered. The last chapter deals with trauma of the globe, localization of foreign bodies and their removal, radium and roentgen-ray therapy, glioma retinae and plastic repair of tumor sites.

In this very comprehensive work on ophthalmic surgery practically all worth-while operations are described in detail and where necessary are illustrated.

The author is to be congratulated on this volume which fills a much needed place in the American literature on ophthalmology.

H. F. G.

Experience in the Management of Fractures and Dislocations. By the Staff of the Fracture Service, Massachusetts General Hospital, Boston. Under the general editorship of PHILIP D. WILSON, M.D. 1036 pages; 26.5 × 18.5 cm. J. B. Lippincott Co., Philadelphia. 1938. Price, \$15.00.

The thousand page volume, "Experience in the Management of Fractures and Dislocations," by Wilson endeavors to simplify, as nearly as possible, the treatment of skeletal injuries and the practical application of the various appliances that are now in vogue. The treatise deals with the actual study of cases and analyzes the results both immediate and late. The data compiled by some 30 odd writers along with methods of treatment for each individual fracture make this work probably one of the most inclusive of any single volume yet written on the subjects of fractures and dislocations. The general practitioner, specialist, and teacher in this important branch of surgery will find this book a valuable reference.

T. B. A.

COLLEGE NEWS NOTES

GIFTS TO THE COLLEGE LIBRARY

Grateful acknowledgment is made of the receipt of the following donations to the College Library of publications by members:

Reprints

Dr. William G. Bernhard (Associate), Newark, N. J.—2 reprints;
Dr. Dean B. Cole, F.A.C.P., Richmond, Va.—4 reprints;
Dr. Willard J. Davies, F.A.C.P., Rockville Centre, N. Y.—2 reprints;
Dr. Harold H. Golz (Associate), Clarksburg, W. Va.—1 reprint;
Dr. J. Edwin Habbe, F.A.C.P., Milwaukee, Wis.—9 reprints;
Dr. A. A. Herold, F.A.C.P., Shreveport, La.—2 reprints;
Dr. Cullen Ward Irish, F.A.C.P., Los Angeles, Calif.—1 reprint;
Dr. Jerome G. Kaufman (Associate), Newark, N. J.—1 reprint;
Dr. Elmer A. Kleefeld (Associate), Forest Hills, N. Y.—1 reprint;
Dr. Louis H. Landay, F.A.C.P., Pittsburgh, Pa.—1 reprint;
Dr. M. B. Marcellus, F.A.C.P., Tillamook, Ore.—1 reprint;
Dr. Leslie M. Smith (Associate), El Paso, Tex.—2 reprints;
Dr. A. C. Woofter (Associate), Parkersburg, W. Va.—2 reprints.

SECTIONAL MEETINGS OF THE COLLEGE

During the autumn months many of the College Governors will conduct sectional meetings of the Fellows and Associates in their territories. Dr. Samuel E. Munson, Governor for Southern Illinois, has announced a sectional meeting of the Illinois members at Jacksonville, Ill., on October 18, when Dr. James H. Means, F.A.C.P., Boston, will be the specially invited guest speaker.

Dr. C. H. Cocke, Governor for North Carolina, has announced a meeting of the North Carolina Fellows and Associates at Chapel Hill and Durham on October 20-21. The North Carolina program was in charge of Dr. Wilburt C. Davison, F.A.C.P., Durham, Dr. William de B. MacNider, F.A.C.P., Chapel Hill, and Dr. Verne S. Caviness, F.A.C.P., Raleigh.

A sectional meeting of the Fellows and Associates residing in the State of Virginia was held at Richmond October 4. Further reports on these meetings will be obtained and published later.

POSTGRADUATE COURSES UNDER AUSPICES OF THE COLLEGE

The Committee on Postgraduate Education and the Board of Regents will later announce the program of postgraduate courses to be offered under the auspices of the American College of Physicians during the winter and spring of 1940. Heretofore, these courses have been organized at various centers conveniently reached on the way to the Annual Session of the College and have consisted of two weeks' intensive work just preceding the Annual Session. The College made these courses available to its members at minimum cost, the College itself assuming full responsibility for promotion, advertising, printing and registration. This activity of the College will be in its third year, and due to the acclaim from those who have taken the courses

during 1938 and 1939, the program will be continued. However, the Board of Governors of the College, through its Committee on Postgraduate Survey, headed by Dr. Henry M. Thomas, Jr., F.A.C.P., Baltimore, has initiated a careful study of the whole problem—the types of courses, the time when courses shall be given, means of improving the courses, etc.—with the purpose in view of making helpful recommendations to the official Committee on Postgraduate Education, headed by Dr. Hugh J. Morgan, F.A.C.P., Chairman, Vanderbilt University Hospital, Nashville, Tenn. Suggestions concerning these courses will be welcomed by the Committee. Members are urged to communicate their suggestions and recommendations directly to Dr. Morgan.

HOUSE COMMITTEE OF THE COLLEGE SOLICITS SUGGESTIONS

In the Board Room of the Headquarters of the American College of Physicians, Philadelphia, there is a wall space above a mantle, 43" broad and 36" high, which offers a splendid opportunity for an original painting or etching. The Board Room is finished in oak paneling, and the proposed painting will be the high light of the room. The House Committee desires suggestions from the membership at large, in order that an appropriate and dignified work of art may be obtained. One suggestion might represent some event in the development of medicine, preferably occurring in North America. Another possibility might be found in some historical event of importance in connection with the origin and growth of the College. The House Committee will appreciate suggestions regarding the type and subject of the proposed painting. It is also quite possible that some member might desire to underwrite the production of an appropriate subject.

Kindly address communications to the Chairman of the House Committee, Dr. Edward L. Bortz, 2021 W. Girard Ave., Philadelphia, Pa.

Dr. George H. Gehrman, F.A.C.P., Wilmington, Del., was a guest speaker at the fifth Clinical Congress of the Connecticut State Medical Society at New Haven, September 19–21, his subject being "Industrial Poisons."

Northwestern University Medical School, through its Department of Industrial Medicine, conducted its third annual Symposium on Industrial Disease and Hygiene at Chicago on September 25–26. Dr. Herman O. Mosenthal, F.A.C.P., New York, and Dr. James P. Simonds presented a paper on "Kidney Diseases of Midlife"; Dr. Ernest E. Irons, F.A.C.P., Chicago, and Dr. Hollis E. Potter presented a paper on "Nontuberculous Pulmonary Diseases"; Dr. Walter L. Bierring, F.A.C.P., Des Moines, was the speaker at the banquet, his subject being "The Past and Future of Preventive Medicine."

Under the Presidency of Dr. John W. Scott, F.A.C.P., Lexington, the Kentucky State Medical Association held its annual meeting at Bowling Green, Ky., September 11–14. Among guest speakers and their subjects were:

Dr. Roger I. Lee, F.A.C.P., Boston, "Treatment of Artificial Menopause";
Dr. Louis Hamman, F.A.C.P., Baltimore, "Problems in Hematological Diagnosis";
Dr. Milton B. Cohen, F.A.C.P., Cleveland, "Newer Concepts of Allergy."
Dr. Frank A. Simon (Associate) and Dr. Adolph B. Loveman (Associate), both of Louisville, with Dr. Cohen and others, appeared on the Allergy Symposium program, and Dr. J. Murray Kinsman, F.A.C.P., Louisville, gave an address on "Sulfapyridine Indications, Bad Effects and Methods of Administration."

The Michigan State Medical Society held its annual meeting at Grand Rapids September 18-22, under the Presidency of Dr. Henry A. Luce, F.A.C.P., Detroit. Dr. Rock Sleyster, F.A.C.P., Wauwatosa, Wis., President of the American Medical Association, delivered the Andrew P. Biddle Oration (founded by Dr. Andrew Porter Biddle, F.A.C.P., Detroit). Dr. Biddle himself presented the Biddle Oration Scroll to Dr. Sleyster.

Among the guest speakers also appeared Dr. Jonathan C. Meakins, F.A.C.P., Montreal, Que., "Gastrointestinal and Hepatic Function in Congestive Circulatory Failure" and Dr. Maxwell Finland, F.A.C.P., Boston, "Treatment of Pneumonia with Sulfapyridine and Specific Serum."

Among the guest speakers appearing on the program of the ninety-eighth annual meeting of the State Medical Society of Wisconsin in Milwaukee, September 13-15, were the following:

Dr. Edward L. Tuohy, F.A.C.P., Duluth, Minn., "The Relation of Alcohol to Liver Damage" and "An Adequate Dietary in Later Life";
Dr. August A. Werner, F.A.C.P., St. Louis, "The Sex Hormones";
Dr. Alexander E. Brown, F.A.C.P., Rochester, Minn., "Sulfanilamide, Neoprontosil and Sulfapyridine and Their Clinical Applications";
Dr. Rock Sleyster, F.A.C.P., Wauwatosa, Wis., "The Sick Man as a Person";
Dr. Thomas J. Dry (Associate), Rochester, Minn., "Pulmonary Hypertension and Right Heart Failure."

At the last annual meeting of the New Jersey Medical Society at Atlantic City Dr. Berthold S. Pollak, F.A.C.P., Medical Director of the Hudson County Tuberculosis Hospital, Jersey City, received a citation and plaque, presented by this Society. Beneath the seal of the State Medical Society the plaque bears this inscription:

"Presented to Dr. Berthold S. Pollak for his work among the tuberculous, not only of his own county but of the State and nation, for the reflected credit accruing to our State Medical Society from his altruistic activities—1939."

The citation is one of four, the first ever to be granted specifically for work in tuberculosis by the Medical Society of New Jersey in its long history.

Dr. Albert B. McCreary (Associate), Jacksonville, Fla., has been appointed State Health Officer for Florida, succeeding the late Dr. Wilbur A. McPhaul.

At the Kentucky State Fair, Louisville, the University of Louisville School of Medicine presented a public exhibition, the specimens being taken from the pathology museum and arranged under the direction of Dr. Aura J. Miller, F.A.C.P., Professor and Head of the Department of Pathology and Serology in the Medical School.

Among the guest speakers at the seventeenth annual fall clinical conference of the Kansas City Southwest Clinical Society, October 2-5, were the following:

Dr. W. Edward Chamberlain, F.A.C.P., Philadelphia, Roentgenology;
Dr. Elliott P. Joslin, F.A.C.P., Boston, Internal Medicine;
Dr. Russell L. Haden, F.A.C.P., Cleveland, Internal Medicine;
Dr. Rock Sleyster, F.A.C.P., Wauwatosa, Wis., Psychiatry;
Dr. Howard B. Sprague, F.A.C.P., Boston, Internal Medicine.

Dr. Fletcher B. Taylor (Associate), Oakland, Calif., addressed the Nevada State Medical Association at its annual meeting in Reno September 22-23 on "Medical Follies of 1938."

Dr. Grant Thorburn, F.A.C.P., New York City, presided over the symposium on silicosis at the Cornell University Medical College, October 11, held under the auspices of the Tuberculosis Sanatorium Conference of Metropolitan New York.

Dr. Henry H. Turner, F.A.C.P., Oklahoma City, has been promoted to Associate Professor of Medicine on the faculty of the University of Oklahoma School of Medicine, as recently announced by the Dean, Dr. Robert U. Patterson, F.A.C.P.

Among promotions and appointments on the faculty of the Jefferson Medical College of Philadelphia recently announced appear Dr. Garfield G. Duncan, F.A.C.P., Associate Professor of Medicine, and Dr. Creighton H. Turner (Associate), Associate Professor of Medicine.

The twenty-sixth annual meeting of the Mississippi Valley Tuberculosis Conference and the Mississippi Valley Sanatorium Association was held at Omaha, September 20-22. Dr. Hyman I. Spector, F.A.C.P., St. Louis, was President of the tuberculosis conference and Dr. William J. Bryan (Associate), Rockford, Ill., was President of the sanatorium association.

The Mississippi Valley Medical Society conducted its annual session at Burlington, Iowa, September 27-29. Dr. Harold Swanberg, F.A.C.P., Quincy, Ill., is Secretary. Among speakers on the program appeared the following Fellows of the College:

- Dr. Charles Hugh Neilson, St. Louis, "Functional Disease" and round table discussion on "Private Practice in the Hospital";
 - Dr. Alphonse McMahon, St. Louis, "Emergency Treatment of Heart Failure";
 - Dr. Daniel L. Sexton, St. Louis, "Endocrine Therapy: Its Application in General Practice";
 - Dr. Rock Sleyster, Wauwatosa, Wis., "The Sick Man as a Person" and "Medical Problems of the Day";
 - Dr. Fred M. Smith, Iowa City, Iowa, "Treatment of Cardiac Failure" and "The Treatment of the More Common Gastro-Intestinal Disorders";
 - Dr. James H. Hutton, Chicago, banquet speaker;
 - Dr. N. S. Davis, III, Chicago, "Treatment of the Patient Who Has a Hypertensive Cardiovascular-Renal Disease";
 - Dr. Arthur L. Smith, Lincoln, Nebr., "Cardiac Arrhythmias and Murmurs."
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Dr. Shailer U. Lawton, F.A.C.P., New York City, and Dr. Edmund Jacobson, F.A.C.P., Chicago, will cover the fields of Mental Hygiene and Relaxation, respectively, in connection with a survey course in fundamentals of health education, which began at Boston University School of Education September 25 and will continue until January 22.

Dr. Merle D. Bonner (Associate), Superintendent of the Guilford County Tuberculosis Sanatorium, Jamestown, N. C., was recently honored by the Guilford County Medical Society, which presented to him a silver plaque in recognition of outstanding medical work during the year. Dr. William de B. MacNider, F.A.C.P.,

Dean of the University of North Carolina School of Medicine, was the principal speaker.

Dr. Rufus S. Reeves, F.A.C.P., was installed as President of the Philadelphia County Medical Society on September 20, succeeding Dr. Francis F. Borzell.

Dr. Conley H. Sanford, F.A.C.P., has been appointed Professor and Head of the Department of Medicine at the University of Tennessee College of Medicine, Memphis, succeeding Dr. James B. McElroy, F.A.C.P., who has resigned because of ill health. It is reported that Dr. McElroy, however, will continue as Professor. Dr. Lucius C. Sanders, F.A.C.P., has been made Assistant Professor of Medicine.

Dr. Harry Walker, F.A.C.P., has been promoted to Associate Professor of Medicine on the faculty of the Medical College of Virginia, Richmond.

Dr. Burt R. Shurly, F.A.C.P., Detroit, was the guest of honor and delivered an address before the forty-fourth annual meeting of the American Academy of Ophthalmology and Otolaryngology, Chicago, October 8-13.

Dr. W. Bernard Kinlaw, F.A.C.P., formerly of Rocky Mount, N. C., is now established in the practice of Cardiology and Internal Medicine at 195 Hempstead Ave., Rockville Centre, N. Y.

OBITUARY

DR. C. HERBERT BELKNAP

The untimely death of Dr. C. Herbert Belknap—the result of an automobile accident, May 4, 1939—was a great shock to his many friends in the profession.

A man of modest mien, kindly in nature, always with a pleasant smile and a cheery word, he was very popular with his confrères.

The esteem in which he was held, both by the medical profession and his patients, was evidenced by the large number in attendance at his funeral.

Dr. Belknap had perhaps one of the largest practices in Detroit. Born November 5, 1891, at Eden, N. Y.; B.S. degree, University of Illinois, 1911; M.D., Detroit College of Medicine (Wayne University), 1916; Intern, Grace Hospital, 1916-17; Assistant in Physiotherapy Service, 1926-29, Grace Hospital; Assistant Attending Physician, 1932-35, Grace Hospital; Associate Attending Physician, 1935 to date of death, Grace Hospital; Vice Chief, Department of Hyperthermia, Grace Hospital.

Dr. Belknap served two years in the U. S. Army—discharged with the rank of Captain (M.C.) U. S. A., August 1, 1919.

C. Herbert Belknap was elected Associate of the American College of Physicians at the New Orleans Session, April 1939. While in New Orleans he was married to Miss Buchanan, and had been home but a short time before his untimely death.

GEORGE BARRIE HOOPS, M.D., F.A.C.P.

ANNALS OF INTERNAL MEDICINE

VOLUME 13

NOVEMBER, 1939

NUMBER 5

VITAMINS IN THEORY AND PRACTICE*

By HOWARD B. LEWIS, PH.D., *Ann Arbor, Michigan*

OUR conception of the vitamins has undergone material change since the term was introduced into the literature of the biological sciences and medicine by Casimir Funk in 1912. In an important review of the existing knowledge of beri-beri, scurvy, and pellagra, he emphasized the reality of the deficiency diseases and suggested the term "vitamine" for the factors, as yet poorly characterized, which were effective in the cure or prevention of these conditions. The term was intended to suggest their vital function (*vita*, life) and basic nature (amine, a basic compound containing nitrogen). Since early investigations failed to support Funk's contention of the basic nature of vitamin in general, the final "e" was dropped by common consent, and to avoid what appeared to be an unjustifiable connotation, the spelling vitamin was adopted. It is perhaps not without interest to note that 15 years elapsed before the presence of nitrogen in any vitamin was demonstrated. Several of the vitamin factors are now recognized as compounds of nitrogen and the correctness of Funk's term for certain vitamins is thus established.

The term vitamin entered the medical literature as a negative factor, i.e., the vitamins were considered to be substances, preventive or curative, of certain diseases of unknown etiology and hence were designated as anti-neuritic, antiscorbutic and the like. Particularly striking was the fact that the effects obtained by the use of these new dietary factors were far more marked than those shown by corresponding amounts of the more common nutrients (fats, carbohydrates, proteins and salts) and quite out of proportion to the amounts evidently present in the food. The importance of the "little things in nutrition" (Mendel) was thus realized. With the development of the modern science of nutrition came the recognition that these factors, originally defined in relation to pathology, were essential for the maintenance of the normal state of well-being of the organism. Our point of

* Read at the New Orleans meeting of the American College of Physicians March 27, 1939.

From the Department of Biological Chemistry, Medical School, University of Michigan.

view in the study of vitamins thus changed from the negative aspect (they were no longer "anti—s"), to the positive (they were requisite factors for normal nutrition).

With the clearer recognition of the chemical nature and properties of the vitamins, the term "chemical regulators" as applied to this group has become significant. The characterization of the hormones as "chemical messengers" (Bayliss and Starling) or chemical regulators, definite chemical factors for the integration of the reactions of the various organs and tissues, has long been accepted. It seems probable that, in the near future, vitamins may be best characterized as chemical regulators of *exogenous* origin, in contrast to the hormones, chemical regulators of *endogenous* origin. Thus the higher forms have the power to synthesize the hormones, thyroxine, insulin or the various sex sterones, with relative ease from precursors, at present not definitely known but presumably of lesser complexity. The vitamins or exogenous chemical regulators, on the other hand, must be made available to the higher organisms as such or in the form of closely related precursors, i.e., the provitamins. The fact that a supply of preformed vitamins or precursors in the diet is not essential for some species is recognized, but its explanation is not clear. Thus the white rat does not require ascorbic acid (vitamin C) in the diet and since the tissues of these animals contain the vitamin, its synthesis by this species must be assumed.

The original vitamin nomenclature was an alphabetical one, the order being with few exceptions primarily that of the discovery or recognition as an individual factor. This alphabetical nomenclature was further modified by qualifying adjectives indicating simple properties, fat- or water-soluble, heat-labile or heat-stable, and by adjectives suggesting the pathological condition occasioned by the absence of the vitamin from the diet. As our knowledge of the chemistry of the vitamins was extended by isolation, identification and synthesis, the older indefinite names have been replaced by more specific ones. Thus the water-soluble anti-scorbutic vitamin C has been designated as ascorbic acid by Szent-Gyorgyi, who was one of the first to isolate it in pure form. Similarly the heat-stable growth-promoting fraction of the B complex, B₂ or G, is now known as riboflavin.

A primary requirement for progress in the study of vitamins has been the successful experimental production of the deficiency disease in laboratory animals. With such a procedure available, it has been possible to study the occurrence and distribution of vitamins in natural foodstuffs by the use of biological assays based upon effectiveness in the prevention or cure of the associated deficiency disease. Foods were thus characterized as rich, good or poor sources of vitamins. Such classifications were, of necessity, crude since the importance of standardization of experimental procedure was not realized. Ultimately uniform methods of assay were adopted and units of vitamin content which permitted more exact comparison of results from different laboratories were agreed upon. The basis of these units was, however, a biological one; the unit was defined in terms of animal behavior

(growth response, curative or preventive effect) and no absolute evaluation of the various units was possible.

It was evident that if the vitamin theory was to be placed upon a scientific basis, more exact chemical knowledge of their nature and properties was necessary. The studies of the distribution of vitamins in nature had shown in many instances foodstuffs unusually rich in their vitamin content and thus suggested materials from which success in the isolation of the vitamin might be anticipated. Valuable information as to probable chemical properties was provided by investigations of the stability of the vitamins, particularly towards heat and oxidation.

The isolation of the pure vitamin, the determination of the chemical structure and the laboratory synthesis of the vitamins have now been achieved in several instances. The progress in this field since the isolation and chemical characterization of vitamin C (ascorbic acid) in 1933 is notable.

With the knowledge of the chemical nature of the vitamin, chemical assays of the vitamins have in many cases replaced the slow and difficult methods of biological assay. No longer is the vitamin unit defined exclusively in terms of animal behavior but in absolute terms of the content of a specific chemical substance. With such methods available, it has been possible to assay materials which did not readily lend themselves to the methods of biological assay. The vitamin content of blood and tissues, the storage and excretion under physiological and pathological conditions, and the relation of the supply of vitamins in the diet to the maintenance of the vitamin balance may now be determined rapidly and conveniently. If the methods of chemical analysis prove to be as specific as is expected, detailed knowledge of the vitamin economy of the organism should be possible, knowledge as exact as that now obtainable for such simple chemical elements as chlorine or calcium. However, until such a specificity of the methods of chemical assay is conclusively demonstrated, recourse must still be had to the specific animal tests in order to check the chemical tests and to avoid any misinterpretation of the latter.

With the clarification of the problem of the chemistry of the vitamins, the investigations now turn again to the biological aspects. What are the functions of the vitamins? If they are to be regarded as exogenous chemical regulators, what is the basis, chemical and physiological, for the function of each? How are these functions altered in disease? How are the vitamins related to the endogenous chemical regulators, the hormones? Why does a group of atoms, combined in a definite molecular structure, manifest a highly specific physiological activity? To what extent will modification of this chemical structure alter the physiological activity? Will it be possible by the methods of synthetic organic chemistry to obtain compounds superior in activity to the naturally occurring substances? These are unsolved problems, common to both vitamin and hormone studies. They represent one phase of the general problem, the relation of chemical constitution to physiological action. The solution will not be simple, but we may anticipate marked progress.

As had been predicted from the behavior of the vitamin in plant juices, ascorbic acid was a strong reducing agent and, by oxidizing agents, was converted to an oxidation product with a loss of antiscorbutic properties.

It was now possible to seek for a chemical method of assay to replace or supplement the biological assay (production or cure of scurvy in young guinea pigs). Tillmans had made use of the reduction of a dyestuff in order to determine the freshness of fruit juices. It is now known that ascorbic acid reduces readily certain reversible dyes of high oxidation potential (notably *p*-dichlorophenolindophenol). It is thus possible to determine the vitamin C content of a plant or animal tissue by titration with the dye. While the method is not absolutely specific, parallel assays by the chemical and biological methods have demonstrated the value of the chemical procedure.

By the use of this chemical method, the ascorbic acid content of urine, blood and animal tissues, materials which are unsuited for biological assay, may be determined. It has also been shown that this procedure may be applied to histochemical studies. The methods of histochemistry, developed in the Carlsberg laboratories in Denmark, whereby analysis of microtome sections of tissue are possible, have been employed with certain animal tissues (adrenals, pituitary) by Glick. The concentrations of ascorbic acid in the various regions of the glands, the relative numbers of cells in the sections and the vitamin content per cell have been estimated. The contrast between the data of 1929, in which the vitamin C content of the foodstuffs was characterized by such approximations as 0 to + + + +, and those of 1939, in which the content of ascorbic acid *per cell* in various zones of organs is stated in chemical terms, is convincing evidence of the progress in vitamin study and of the validity of the vitamin theory. It must be remembered that not until 1919 was the concept of scurvy as a specific vitamin deficiency disease generally accepted. The existence of subacute vitamin deficiency is now generally recognized and the importance of tests which would permit prompt recognition of these states of sub-optimal nutrition is obvious. Studies of urinary excretion of vitamin C have indicated marked individual variations and have suggested that the degree of saturation of the tissues with ascorbic acid is an important factor in determining urinary excretion. The ascorbic acid content of the blood and urine may be abnormally low when the intake of ascorbic acid is significantly less than the normal requirements. As the intake of ascorbic acid is increased and as the state of tissue saturation is approached, the urinary excretion shows progressive increase until, at saturation, an abrupt rise in the ascorbic acid of the urine is noted. The amount of dietary ascorbic acid necessary to induce saturation appears to be an index of the vitamin C nutrition of the individual. While all workers are not in entire agreement as to the details of such a test, it appears to be of real value in the study of subacute scurvy.

What is the function of ascorbic acid in the animal organism? It appears to be most concentrated in actively functioning tissues, the cortex of

the adrenals, hypophysis, thyroid, corpus luteum and other glands. Its strong reducing action suggests a relation to oxidative processes, to cell respiration. With the chemical background well established, advances in our knowledge of the function of ascorbic acid and of its relation to other vitamins and hormones may be anticipated.

The story of the development of our knowledge of the other vitamins is similar to that outlined for ascorbic acid. New concepts are being introduced. A multiplicity of vitamin factors is suggested. Until investigation has shown the presence of a specific chemical agent of known structure, the existence of a vitamin factor must be questioned. Three components of the water-soluble vitamin B, now referred to as the B complex, have been isolated in crystalline form and the existence of several others has been suggested. B₁, the antineuritic vitamin (thiamin or aneurine), B₂, the growth-promoting factor (G or riboflavin) and nicotinic acid, important in the treatment of human pellagra, are all well characterized.* Each seems to be an essential component in an important enzyme system in nature. It is of interest that the inability to reproduce experimentally in animals the pathology of human pellagra delayed progress in the recognition and treatment of pellagra as a deficiency disease. Chemical methods for the determination of thiamin and nicotinic acid have been presented and valuable information concerning the saturation of the tissues and the urinary excretion of these vitamins will shortly be at our disposal.

The nutritional and chemical backgrounds for continued vitamin investigations are available. The vitamins, natural or synthetic, are readily obtainable. It is for the clinician to make use of the information supplied by the investigations of experimental biology, both for the maintenance of normal nutrition and for the treatment of the deficiency diseases, acute and subacute. The place of vitamins in *normal nutrition* is concerned with their rôle as components of the natural foodstuffs. Careful selection of the diet should make possible an abundant supply of these important essentials. The rôle of vitamins in conditions of *acute deficiency* is that of drugs, by means of which the vitamin balance of the organism shall be restored to normal as rapidly as is possible.

There is, however, a grave danger that in our enthusiasm over the achievements, experimental and clinical, in the vitamin field, we forget that the vitamins comprise only one group of the many substances essential for the normal nutrition and that all the vitamins of the alphabet cannot make good a deficiency in the other important dietary constituents, minerals, protein, fats and carbohydrates. We would do well to bear in mind the warning of Professor Sherman of Columbia University with reference to excessive zeal in the use of vitamin D: "Confidence in the value of the anti-rachitic vitamin must not lead to any lack of care in providing a liberal supply of calcium and phosphorus during growth."

* Since this paper was presented, the isolation and synthesis of crystalline vitamin B₆ has been successfully achieved. This compound, like nicotinic acid, is a pyridine derivative.

A DISCUSSION OF A THERAPEUTIC TEST AND A PROVOCATIVE TEST IN GOUTY ARTHRITIS *

By L. MAXWELL LOCKIE, M.D., F.A.C.P., *Buffalo, New York*

THE first part of this paper will be devoted to a discussion of the effect of colchicine on gouty arthritis. The second part concerns the use of a diet high in fat, low in carbohydrate, and low in protein as a means of provoking attacks of gouty arthritis in some gouty patients.

During the past 10 years the physicians of the United States have realized the apparent increase in the number of cases of gout and the occurrence of a symptom of gout—namely gouty arthritis. Before the work of Hench,¹ it was thought by many to be a disease which existed only in Europe, especially in England. Now, woe betide the physician who does not consider gout very seriously in every male patient who complains of arthritis. It is estimated that 96 to 98 per cent of gouty arthritis occurs in males. The most important single aid in the diagnosis is the history of recurrent arthritis with complete relief from symptoms between attacks. Particular emphasis must be placed on the words "complete relief." The joint symptoms of rheumatic fever also vanish completely but that disease usually occurs before the age of 25 years whereas gouty arthritis most frequently occurs after 25 years of age. Tophi containing sodium urate crystals are found only in gout. The blood uric acid may be increased above 5 mg. per cent in the early cases and is usually increased in the later cases. Roentgen-ray findings, provocative and therapeutic tests may be helpful.

There are a few drugs used in medicine which act specifically in the treatment of disease; for example, quinine in malaria. Colchicine is a drug which quickly relieves the acute symptoms of gouty arthritis. It has been used for thousands of years—mention of it is made in the Ebers Papyrus 1550 B.C. During the past 75 years the wine of colchicum, which contains colchicine as the active ingredient, has been preferred, but more recently the tablets of the alkaloid colchicine are widely used. A more accurate dosage is available in the tablet form. The mode of action of colchicine is not known.

In the experiments the drug was given in divided doses over a period of 24 to 72 hours until the patient had diarrhea. This was considered to be a sign that a full dose had been administered. Diarrhea often occurred after very few doses of one milligram (gr. 1/60), whereas others could take the drug for several days before the catharsis occurred. The drug was discontinued after the onset of the diarrhea.

* Read at the New Orleans meeting of the American College of Physicians March 30, 1939.

From the Buffalo General Hospital and the University of Buffalo Medical School.

One hundred and twenty-five cases were studied. One group consisted of 75 private patients with proved gouty arthritis and the other group was composed of 50 patients with other forms of arthritis taken from the Arthritis Clinic of the Out-Patient Department of the Buffalo General Hospital. Tophaceous and non-topaceous gout were included. The diagnosis was made according to the criteria described by Hench.¹ All patients, except those few seen in the first attack, had a typical history of recurrent arthritis with complete relief from signs and symptoms between attacks. Tophi, when present, were examined for sodium urate crystals before they were considered to be diagnostic of gout. The blood uric acid usually was above 5 mg. per cent. The response to colchicine was uniform in the group of gouty patients. All experienced marked relief of the acute symptoms, beginning about the time of the diarrhea. Instead of continually shifting in an effort to find a more comfortable position the patient could now move the involved joint with less pain. The sensitiveness of the skin around the joint was markedly decreased. Although the patient became much more comfortable not all of the symptoms were gone within 24 hours. During the next few days the stiffness and aching usually disappeared. Many of these patients had taken other forms of medication with little relief. Practically all had used acetylsalicylic acid or sodium salicylate with transient improvement only. Cinchophen was used by some and gave more relief than the acetylsalicylic acid. Three patients had marked urticaria and swelling following administration of the cinchophen. All noticed that the relief from colchicine was far more effective than from either the salicylate or cinchophen preparations.

The 50 patients from the Arthritis Clinic of the Buffalo General Hospital with various forms of arthritis other than gouty arthritis were given full doses of colchicine. They had been given acetylsalicylic acid or sodium salicylate medication previous to this study. The colchicine was given in a large enough quantity so that all the patients had diarrhea within 72 hours.

The cases of arthritis were divided as follows:

Atrophic (rheumatoid or chronic infectious)	21 cases
Hypertrophic (osteoarthritis)	14 cases
Menopausal	7 cases
Spinal (not hypertrophic)	5 cases
Gonorrheal	1 case
Fibrositis	2 cases

In no case of arthritis was there a dramatic relief of symptoms. A few had transient, mild relief during the active state of catharsis but the next day the pain returned with all of its former severity. No patient experienced enough relief to want to take the drug again. Those patients with the shoulder muscle pain of menopausal arthritis and fibrositis seemed to have comparatively more relief than others studied in this group.

A chart showing the effect on pain is given below.

Effect on Pain	No Relief	Slight Relief	Marked Relief
Gouty arthritis.....	0	0	75
Atrophic arthritis.....	17	4	0
Hypertrophic arthritis.....	14	0	0
Menopausal arthritis.....	3	4	0
Spinal arthritis.....	3	2	0
Gonorrheal.....	1	0	0
Fibrositis.....	0	2	0

In summary, colchicine acts in an unknown manner in the human body. It has a specific therapeutic effect in relieving the symptoms of gouty arthritis. There may be a mild transitory relief in some of the other forms of arthritis but it is never marked nor lasting.

The second part of this study is concerned with the precipitation of attacks of gouty arthritis by means of a special diet. In 1935 Lockie and Hubbard² reported studies on four patients with gouty arthritis to whom a high fat diet had been given. This work was suggested by the observations of Harding³ who noted an increase of the blood uric acid in patients on a diet low in carbohydrate, low in protein and high in fat content. Lennox⁴ noted the same effect in patients in a starvation state.

The experiments reported in 1935 will be briefly summarized as well as the results of five similar experiments carried out within the past six months.

Conditions of the experiments:

1. Positive diagnosis of gout with gouty arthritis.
2. No attack to be expected at the time.
3. No medication with the salicylate or cinchophen groups for two weeks previously.
4. Diet:
 - Low in carbohydrate
 - Low in protein (low in purine)
 - High in fat
5. Codeine used only for relief of pain.

Experiment 1: E. H., a man, aged 52, had recurrent gouty arthritis of the feet, knees and hands since 1912. There was complete recovery between attacks. Tophi containing sodium urate crystals were removed from the left ear lobe. The blood uric acid was 6.0 mg. per cent (whole blood method).

The interval between attacks of gouty arthritis had been approximately a year. After a period of two weeks had elapsed following the present attack, he was given a diet of C 50, P 50, and F 220. On the seventh day there was marked pain, swelling and tenderness in the joints of the feet and ankles. The uric acid rose from 5.5 mg. per cent to 8.0 mg. per cent. Four days later the diet was changed to C 380, P 60 and F 130. Within two days marked improvement took place. The blood uric acid continued to remain elevated for 14 days, then gradually fell to the preexperimental level. There was no further exacerbation of pain.

Experiment 2: W. R., a man, aged 28, had recurrent gouty arthritis for four years, usually following strenuous exercise, alcoholic debauch or thorough chilling. He

stated that during an attack there was marked swelling, pain and tenderness which would disappear within 10 to 14 days. The blood uric acid was 6.2 mg. per cent at the time of his last attack.

After recovery from this flare-up he stated, judging from past experience, that he would not have another attack for some months. Consequently we felt justified in administering the diet of C 60, P 60 and F 230 one week after recovery from this last attack. Within three days he felt poorly, the left hand, knee and small joints of the left hand became swollen and painful. It was necessary for him to go back to bed. No medication was given but the diet was changed to C 400, P 70 and F 60. There was marked improvement in 48 hours. He had no other attack of gouty arthritis during the next five months, at the end of which time he left the city.

Experiment 3: A. A., a man, aged 74, had recurrent gouty arthritis during the past 23 years. The blood uric acid was 6.8 mg. per cent. No tophi were present. Intervals between attacks were at least 10 months.

At the end of one week he was given a diet of C 20, P 30 and F 300. Within 48 hours the foot became swollen and tender. No medication was given but the diet was changed to C 350, P 60 and F 8 and within 72 hours all signs and symptoms had disappeared.

Experiment 4: After the above-mentioned patient had been free of pain for one week he agreed to resume the diet with the high fat content. Within 48 hours he had another attack and following a change to the diet containing the high carbohydrate proportion he became entirely well. There was little change in the blood uric acid during this experiment, possibly owing to the fact that he was on the high fat diet such a short time.

Experiment 5: N. G., a boy, aged 16 years, had tophi in both ears in 1932. Two years later he experienced his first attack of gouty arthritis. Three similar episodes occurred within three months. When he was seen three months following the initial attack he had many tophi containing sodium urate. The blood uric acid was 7.6 mg. per cent.

A week following recovery from the last attack he was given a diet of C 50, P 50 and F 250. At the end of 13 days he developed a very severe attack of gouty arthritis involving many joints. The blood uric acid increased from 8.6 mg. per cent to 16.0 mg. per cent. A diet high in carbohydrate did not alter the blood uric acid but within two days the patient felt better. It was necessary to give sodium salicylate before the blood uric acid returned to the former level.

Experiment 6: E. H., same patient as in experiment 1. During the past four years he was seen in the Out-Patient Department regularly. His diet was high carbohydrate, moderate protein (with low purine) and fairly low fat content. He took acid acetylsalicylic 0.30 gm. (gr. V) four days weekly, and used colchicine if he had any twinges of pain. During this period he had not experienced any severe attacks of arthritis. While convalescing from a cerebral accident he was given a diet of C 50, P 50 and F 250 for five days without provoking a flare-up in his joint symptoms. The patient left the hospital at this time; consequently the experiment could not be continued. However, this case should be included in view of the following experiments in which three attacks of gouty arthritis were produced within 48 hours of the beginning of the high fat diet in other gouty patients.

Experiment 7: J. C., a male, aged 54 years, has had recurrent arthritis with symptomless periods in between. Both big toe joints, ankles, knees, shoulders, elbows and fingers have been involved at various times. There was some limitation of motion of the right ankle due to tophi formation in the small bones. Tophi containing sodium urate crystals were present in the left ear lobe, left olecranon bursa, and on the dorsal surface of the left index finger. The blood uric acid was 5.0 mg. per cent. He had been free of any pain or discomfort from 1933 until November 15, 1938,

at which time he began to notice pain in the left hand and the left shoulder. A diagnosis of gouty arthritis was made.

On December 15, 1938 he was given a diet of C 35, P 50 and F 250. Within 48 hours he had severe pain in the right knee, right ankle and left hand, and during the next 24 hours the knee joint became filled with fluid. Two days after the high fat diet was started the temperature, which previously was normal, began to rise until it reached 103° F. on the fourth day of the diet. During this period the patient was so ill he could neither eat nor sleep. It was felt necessary to stop the high fat diet and give all the treatment possible to relieve the extremely severe attack. The pain subsided promptly upon administration of full doses of colchicine and a change to a high carbohydrate diet, but muscular stiffness persisted for a short time. The temperature became normal three days after institution of therapy. The level of blood uric acid did not vary.

Experiment 8: During the following month the above patient felt well. He was again placed on a diet of C 35, P 40 and F 250, and low in purine content. Sixteen days later he had a very severe attack of gouty arthritis involving many joints of the body—especially the right ankle, the left shoulder and the right knee which again filled with fluid during a 12 hour period. Even the area about the tophi in the left ear was very sensitive. The body temperature again began to rise, reaching a peak of 102° F. within three days; with change of diet to C 350, P 50 and F 70, and colchicine in full doses, his temperature gradually returned to normal within three days and his symptoms were relieved. There was little fluctuation of his blood uric acid during this time.

Experiment 9: N. G., the same patient as in experiment number 5. He had been quite comfortable during the following four years except for a steady progression of tophus formation. No severe attacks had occurred during the past year. He was admitted to the hospital for correction of deformity of the right knee joint as the result of tophus. During the first 24 hours the patient was given a high carbohydrate diet, then it was changed to C 43, P 30 and F 180. After 48 hours he began to be restless and felt poorly. The body temperature began to rise and he had extreme pain in many joints. Within three days the temperature had reached 102.4° F. and the pain had become more severe. The diet was changed to C 200, P 30 and F 35, and colchicine was given in large doses. The temperature dropped to normal within 48 hours and the patient was comfortable. There was a slight increase in the blood uric acid.

Experiment 10: The same patient was given a high fat diet after a period of 10 days during which time he had had no pain, nor was any medication used. Again within 48 hours his temperature began to rise and he had severe pain in many joints. This became progressively worse so that at the end of another 48 hours his temperature was 101.2° F. and many joints of his body were involved. He had pain around the tophi in the left ear. Again the diet was changed to one high in carbohydrate and low in fat content. Full doses of colchicine were given and within 48 hours his symptoms disappeared. During this time his temperature became normal. No further medication was necessary.

CONCLUSIONS

1. Colchicine in sufficient doses to cause diarrhea relieves the signs and symptoms of gouty arthritis in a dramatic manner.
2. The administration of a low carbohydrate, low protein, high fat diet to patients with gout provoked an acute attack of gouty arthritis in nine of the 10 experiments.

REFERENCES

1. HENCH, P. S., VANZANT, F. R., and NOMLAND, R.: Basis for the early differential diagnosis of gout: a clinical comparison of 100 cases each of rheumatic fever, infectious arthritis and gout, *Collected Papers of the Mayo Clinic and Mayo Foundation*, 1928, xx, 790.
2. LOCKIE, L. M., and HUBBARD, R. S.: Gout: changes in symptoms and purine metabolism produced by high fat diets in four gouty patients, *Jr. Am. Med. Assoc.*, 1935, civ, 2072.
3. HARDING, V. J., ALLEN, K. D., EAGLES, B. A., and VAN WYCK, H. B.: The effect of high fat diets on the content of uric acid in the blood, *Jr. Biol. Chem.*, 1925, lxxiii, 37.
4. LENNOX, W. G.: Increase of uric acid in the blood during prolonged starvation, *Jr. Am. Med. Assoc.*, 1924, lxxxii, 602.

A STATISTICAL STUDY OF ALLERGY IN ARTHRITIS *

By EUGENE F. TRAUT, M.D., and EMIL G. VRTIAK, M.D.,†
Chicago, Illinois

BECAUSE of the similarity of certain aspects of rheumatic fever to serum sickness, the classical example of allergy, we investigated the frequency of asthma, hay fever, urticaria, eczema, migraine, and hyperesthetic rhinitis in 459 victims of the rheumatic state, in the Central Free Dispensary, in Cook County Hospital, Chicago, Illinois, and in private practice. These individuals, living under identical conditions and with foci inhabited by bacteria common to all, have responded with clinical rheumatism to infections, injuries, fatigue or to dietary inadequacies. That these individuals should react with rheumatism to environmental influences apparently identical with those affecting the non-rheumatic population has been said to be due to allergy or hypersensitiveness.^{1, 2} Even gout has been called an expression of hypersensitiveness to food.³

As in the case of Koch's early demonstration in the tuberculin reaction of hypersensitiveness to derivatives of tubercle bacilli, Swift and others have demonstrated hypersensitiveness to other bacterial products. Touart and Thomas⁴ added further evidence of the allergic nature of skin reactions to bacterial products by their demonstration of eosinophiles at the sites of injection. Swift^{5, 6, 7} and his co-workers and Birkhaug⁸ have made animals hypersensitive to the products of non-hemolytic, as well as green or hemolytic streptococci, and again desensitized them. Miller⁹ made rabbits hypersensitive to gonococci. Pilot¹⁰ secured positive skin tests with a filtrate of *Staphylococcus aureus* in patients infected with this organism. Mackenzie and Hanger¹¹ made human beings hypersensitive to the supernatant fluid of streptococcus cultures. Swift's work indicated that foci of infection played a sensitizing rôle.¹² Swift,^{5, 12, 13} Derick,¹⁴ I,¹⁵ and others¹⁶ have found rheumatic individuals hypersensitive to streptococci as judged by skin tests. According to Brown¹⁷ the possibility of food or bacterial allergy should be considered in every case of arthritis. He and others¹⁸ perform skin tests with bacteria and use elimination diets to find the offending agent in arthritis. Harkavy and Hebald¹⁹ report nine instances of arthritis in asthmatics. In eight of these patients the removal of foci relieved the arthritis while simultaneously improving the asthma. According to their presumptions, both syndromes were an expression of hypersensitiveness to the bacteria inhabiting the foci.

* Received for publication December 28, 1937.

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† Deceased.

The conditions noted as occurring in the antecedents of patients with the rheumatic complex belong in that more specific sub-group of allergic states called atopic. In associating certain arthropathies with allergy, we are not specifying bacterial, food, or physical allergy. "Bacterial allergy, as indicated by the indurative skin test, is apparently very different from atopy, which is an hereditary condition and whose expression of allergy is edema. To be sure, under certain circumstances there is a relationship between these two expressions of human hypersensitiveness, but certainly they are not interchangeable."²⁰

The relation of arthritis to allergy may be, as Pilot²¹ has suggested, simply that arthritis, especially of the rheumatoid type, and allergic disease tend to occur in certain labile individuals who react excessively to changes in their environment. Arthritis and allergic symptoms tend to occur in these individuals in whom allergic and arthritic manifestations can be said to have a meeting ground. Rackemann doubts that arthritis can be placed in the same category as asthma, hay fever, eczema or urticaria. His asthma and hay fever patients have rarely had any rheumatic complaints.²² With allergy playing a rôle in rheumatism, the rheumatic population might be composed of a large or preponderant number of individuals having also asthma, hay fever, urticaria, eczema or possibly even migraine or hyperesthetic rhinitis.

METHODS AND FINDINGS

Four hundred fifty-nine patients in the Central Free Dispensary, in the Cook County Hospital and in our private practices were questioned by the same personnel regarding the occurrence, the frequency of such occurrence, and the severity of asthma, hay fever, urticaria and eczema, either in themselves, one or both parents, blood aunts or uncles and in one or both grandparents. Because of the alleged allergic association of migraine³¹ and of hypertrophic rhinitis, as manifested by catarrh, obstructed nose and repeated colds,²⁴ patients were cross-examined for these syndromes. Of these, 359 had rheumatic heart disease, atrophic or hypertrophic arthritis as defined by the American Association for the Study and Control of Rheumatic Diseases, and 100 others (a non-rheumatic group) were chosen at random from the general sick population. We chose these 100 "controls" from sick people to secure a view of allergy's effect in its relation to rheumatism as contrasted with its relation to illness in general.

ALLERGY IN NON-RHEUMATIC PATIENTS

A report of the questioning of these people, sick with a variety of illnesses not rheumatic, forms the basis of our evaluation of the frequency or intensity of allergy in the rheumatic patients. Of these non-rheumatic sick, 3 per cent were afflicted with asthma or hay fever, 2 per cent being asthmatic and 1 per cent admitting hay fever; 13 per cent had had "hives." We feel

that their report of urticarial symptoms is reliable. That 5 per cent of the patients had eczema is open to more question; possibly various cutaneous mycoses would be reported under this heading. However, even in the fungus diseases of the skin, allergy may play a part. It has been our own observation that itching and the size of the fungus growth are usually greater and more persistent in allergic patients. Thus, 19 per cent of our control group are allergic as judged by their being sufferers from asthma, hay fever, urticaria or eczema. A patient having more than one of the allergic syndromes was counted as one person showing allergy. In other words, a patient with urticaria and hay fever was counted as one instance of allergy, the severity and frequency of his allergic manifestations being noted.

Type of Cases	No. of Cases	Percentage of Patients Having								Percentage Having Family History of	
		Asthma	Hay fever	Urticaria	Eczema	Rhinitis	Migraine	Asthma, Hay Fever, Urticaria, Eczema	Asthma Hay fever Urticaria Rhinitis Migraine	Asthma Hay fever Urticaria Eczema	Asthma Hay fever Urticaria Eczema Rhinitis Migraine
Atrophic Arthritis.....	175	5.2	12.6	20.6	8.0	25.1	36.2	18.8	54.1	10.9	12.0
Hypertrophic Arthritis....	129	7.8	16.2	23.2	10.8	37.9	34.8	30.2	61.2	13.9	13.9
Rheumatic Heart Disease.....	55	7.2	10.9	21.8	1.8	Not	ques- tioned	30.9	Not questioned	29.1	Not questioned
Controls.....	100	2.0	1.0	13.0	5.0	14.0	18.0	19.0	37.0	10.0	11.0

Eighteen per cent of this non-rheumatic control group had had sick headaches. The question as to the allergic etiology of all migraine is still debatable. These patients are not to be excluded from the allergic group, even if the sick headache were released by an emotional upset or refractive error. The probability of an allergic constitution is still strong.^{25, 26, 27, 28}

Fourteen per cent of these controls complained of frequent colds, nasal catarrh or stuffy noses. Anatomical deformities of the nasal passages and acute upper respiratory infections were excluded as far as possible. It was assumed, on admittedly debatable grounds, that these symptoms indicated nasopharyngeal hypersensitiveness or hypertrophic rhinitis.

To include migraine and these nasal disturbances would raise the allergic percentage of our controls to 37 per cent.

Eleven per cent of these non-arthritis controls recalled near blood relatives with asthma (6 per cent), eczema (4 per cent), hay fever (2 per cent) and colds and catarrh (1 per cent). Strangely enough, none of them re-

membered any relatives with sick headaches. Such an impressive syndrome as asthma would be calculated to impress itself on their memory. Among such asthmatics there may have been instances of non-allergic cardiac decompensation or, less likely of tuberculosis with dyspnea.

According to expectations, the allergic controls had a higher incidence of familial hypersensitiveness (21 per cent). This was exclusive of migraine and "colds," and is to be contrasted with the 11 per cent of the whole control group admitting allergic disease in their families. The control group complained most frequently of colds and catarrh. Migraine was their next most common "evidence of allergy." Urticaria was more common than eczema, asthma and hay fever combined.

ALLERGY IN THE RHEUMATIC GROUP

According to the patients' stories, allergic manifestations were much more prominent (30.9 per cent) in the 55 patients with rheumatic heart disease. This agrees with the commonly observed similarity of some cases of rheumatic fever and serum disease. The relation of the various expressions of hypersensitiveness persists in this cardiac group, hives being the most common (21.8 per cent). Eighteen per cent of the patients have had either asthma or hay fever. This is a frequency six times as great as that observed in the controls. As contrasted with the relatives of the control patients, more of the patients with rheumatic hearts have a family history of allergy (29.1 per cent). The patients with rheumatic heart disease were not questioned regarding migraine or "colds."

A similarly high incidence of allergic disease was found in that group of chronic rheumatics including hypertrophic (osteo-arthritic) arthritis. The common difficulty in clearly separating the two great groups of chronic arthritics was experienced. Admittedly most of the patients in that group termed hypertrophic and many in the atrophic group could more properly be called "mixed." They were assigned to either file, depending upon a preponderance of those constitutional peculiarities and disease manifestations characteristic of the two great groups. Of the 129 patients with hypertrophic arthritis, 30.2 per cent had had asthma, hay fever, urticaria or eczema. Fewer gave a history of allergy in the family than was the case with rheumatic heart disease. The incidence of migraine in patients with hypertrophic arthritis was almost twice as great as in the controls: 34.8 per cent as compared with 18 per cent.

Contrary to our anticipations, of all the rheumatic syndromes studied, allergic manifestations were least common in atrophic arthritis (chronic infectious, rheumatoid arthritis, arthritis deformans). This atrophic group of the chronic arthritics reported an increased susceptibility to colds as manifested by attacks of coryza. This group also had migraine twice as commonly as the controls. This might be anticipated from Stieglitz's description⁸⁰ of the migrainous constitution. On the other hand, the chronic

arthritics of the opposite or sthenic constitution admitted a similarly high incidence of migraine. Headaches ascribable to the radiculitis consequent upon arthritis of the cervical vertebrae were eliminated as far as possible. Of all the complaints considered, migraine was that most commonly elicited from the entire rheumatic group. Colds and catarrh were next in frequency. As in the controls, hives were much more common than hay fever, asthma or eczema.

SUMMARY

So far as the degree of allergy in a patient or his family is concerned, as estimated by the number of allergic diseases or the frequency and severity of their occurrence in a given patient, or by the closeness and number of allergic relatives, all of the rheumatic groups show from two to three times as much allergy as the controls.

The rheumatic patients exceeded the controls by 200 to 300 per cent in the frequency and severity of the various manifestations of allergy in themselves as well as in the closeness of relationship of allergic relatives.

DISCUSSION

The patient with any of the commonly accepted evidences of past or present rheumatism is distinguished from the rest of the population by his distinctive reactions to bacterial invasion, as well as to climatic changes. The rheumatic is further peculiar in that disturbance of his so-called focal infections, for example by surgery, frequently provokes an aggravation of his illness. His behavior simulates that of the anaphylactic or hypersensitive state. He reacts distinctively to skin tests with bacterial proteins. In addition, the high incidence of allergic manifestations in people with rheumatism is evidence of an increased tendency of the rheumatic to react in an unusual manner (or be hypersensitive) to his environment.

Rackemann estimates the incidence of hypersensitiveness in the general population, as manifested by asthma and hay fever, to be between 0.5 per cent and 1.0 per cent.²² Vaughan²³ believes in an incidence of allergy of 10 per cent in the total population. Of our 100 sick people 3 per cent had asthma or hay fever and 19 per cent had or had had either asthma, hay fever, urticaria or eczema. To include migraine and hypertrophic rhinitis as evidences of allergy would lead to the conclusions that 37 per cent of our general sick population are allergic. The tendency to call upon allergy to explain many and various illnesses not frankly or solely of allergic origin is prevalent. In spite of the tendency of some^{29, 17} to assume an allergic relationship for rheumatoid arthritis and indeed to practice allergic methods in its diagnosis and treatment we found no more evidence of hypersensitiveness in rheumatoid arthritis than in non-rheumatic sick people.

CONCLUSIONS

1. Rheumatic patients have allergic diseases much more commonly than the general sick population.
2. Blood relatives of rheumatics have more allergic disease than the general sick population.
3. Migraine is the most frequent allergic manifestation of all sick people interrogated.
4. Migraine is the most common allergic manifestation of rheumatic patients.
5. Urticaria is more common than asthma, hay fever or eczema in the 459 people questioned.
6. Urticaria is more common than asthma, hay fever or eczema in rheumatic patients.
7. Patients with atrophic arthritis showed less evidence of hypersensitiveness than did the patients with hypertrophic arthritis, or those with a history of previous rheumatic fever.

BIBLIOGRAPHY

1. SWIFT, H. F.: Rheumatic fever, Nelson's loose leaf living medicine, Thomas Nelson & Son, New York City, Volume 1, 1920, Chapter 2, pp. 31-48.
2. POST, W. E.: Focal infection, *ibid*.
3. GUDZENT, F.: Testing and treatment of rheumatism and gout with specific allergens, *Deutsch. med. Wchnschr.*, 1935, lxi, 901.
4. TOUART, M.D., and THOMAS, W. S.: Eosinophilia in bacterial reaction sites, *New York State Jr. Med.*, 1933, xxxiii, 1.
5. HITCHCOCK, C. H., and SWIFT, H. F.: Studies on indifferent streptococci, *Jr. Exper. Med.*, 1929, xlix, 637.
6. HITCHCOCK, C. H., CAMERO, A. R., and SWIFT, H. F.: Perivascular reactions in lung and liver following intravenous injection of streptococci into previously sensitized animals, *Jr. Exper. Med.*, 1934, xlix, 283.
7. SCHULTZ, M. P., and SWIFT, H. F.: Reactions of rabbits to streptococci (comparative sensitizing effect of intracutaneous and intravenous inocula in minute doses), *Jr. Exper. Med.*, 1932, lv, 505.
8. BIRKHAUG, K.: Allergic reactions with a toxin-producing strain of the non-methemoglobin-forming streptococcus isolated from rheumatic fever, *Jr. Infect. Dis.*, 1928, xliii, 280.
9. MILLER, P.: Some observations on the specificity of allergic reactions to certain of the gram-negative diplococci, *Trans. Assoc. Am. Phys.*, 1933, xlviii, 382.
10. PILOT, I.: Discussion of skin reactions with *Staphylococcus aureus*, *Jr. Am. Med. Assoc.*, 1931, xcvi, 878.
11. MACKENZIE, G. M., and HANGER, F. M.: A study of hypersensitiveness to derivatives of hemolytic and non-hemolytic streptococci, *Proc. Soc. Exper. Biol. and Med.*, 1923, xxi, 442.
12. SWIFT, H. F., DERICK, C. L., and HITCHCOCK, C. H.: Bacterial allergy (hyperergy) to non-hemolytic streptococci in its relation to rheumatic fever, *Jr. Am. Med. Assoc.*, 1928, xc, 907.
13. SWIFT, H. F., HITCHCOCK, C. H., DERICK, C. L., and McEWEN, C.: Intravenous vaccination with streptococci in rheumatic fever, *Am. Jr. Med. Sci.*, 1931, clxxxii, 1.

14. DERICK, C. L., and FULTON, M. N.: Skin reactions of patients and normal individuals to protein extracts of streptococci, *Jr. Clin. Invest.*, 1931, x, 1.
15. TRAUT, E. F.: Skin tests with bacterial products in arthritic and non-arthritic individuals, *Jr. Allergy*, 1937, viii, 501.
16. GIBSON, H. J., THOMSON, W. A. R., and STEWART, D.: Hemolytic streptococcus as factor in causation of acute rheumatism, *Arch. Dis. Child.*, 1933, viii, 1.
17. BROWN, G. T.: Allergic phases of arthritis, *Jr. Lab. and Clin. Med.*, 1934, xx, 247.
18. TURNBULL, J. A.: The relation of anaphylactic diseases to arthritis, *Jr. Am. Med. Assoc.*, 1924, lxxxii, 1757.
19. HARKAVY, J., and HEBALD, S.: Quoted by Brown.¹⁷
20. ALEXANDER, HENRY L.: Personal communication.
21. PILOT, I.: Personal communication.
22. RACKEMANN, F. M.: The rôle of allergy in arthritis, *New England Jr. Med.*, 1933, ccviii, 1347.
23. VAUGHAN, W. T.: *Allergy*, 1934, C. V. Mosby Company, St. Louis, p. 68.
24. HARKAVY, J.: Allergic manifestations of the common cold, *Med. Clin. North Am.*, 1933, xvii, 193.
25. RACKEMANN, F.: *Clinical allergy*, 1931, Macmillan Company, New York, p. 133.
26. BALYEAT, R. M., and RINKEL, H. J.: Studies in allergic migraine, *ANN. INT. MED.*, 1931, v, 713.
27. DEGOWIN, E.: Allergic migraine, *Jr. Allergy*, 1932, iii, 447.
28. RINKEL, H. J.: Migraine. Some considerations of allergy as a factor in familial recurrent headache, *Jr. Allergy*, 1933, iv, 303.
29. DORST, S. E., and WHERRY, W. B.: Local skin reactions in the selection of antigens for autogenous vaccines, *Ohio State Med. Jr.*, 1928, xxiv, 539.
30. STIEGLITZ, E. J.: Migraine physique, *Am. Jr. Med. Sci.*, 1935, clxxxix, 359.
31. VAUGHAN, W. T.: *Allergy*, 1934, C. V. Mosby Company, St. Louis, p. 336.

ACTIVE IMMUNIZATION AGAINST TETANUS *

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ACTIVE immunization against tetanus has aroused a great deal of interest among clinicians and public health workers because of its possible use as a preventive measure of general applicability. The antitoxin titer produced by the injection of tetanus toxoid, and the influence exerted upon this titer by such factors as dosage, time interval between injections, associated antigens and "repeat" or stimulating injection of toxoid, have been the subject of careful investigation.¹⁻³² We now wish to add our findings on the comparative value of various antigenic preparations.

Tetanus toxoid (plain) (No. 5969), *tetanus toxoid (plain)* to which 0.4 per cent alum was added (No. 5969-5) and *alum precipitated tetanus toxoid (refined)* (No. 8387-3) were used for active immunization of 32 healthy individuals, 14 to 28 years of age.

Twelve persons (group A) † were immunized by means of three 1.0 c.c. injections of *tetanus toxoid plain* (No. 5969). The period between injections was varied in order to determine the interval of time that will give the best antitoxin response (chart 1). This appears to be one month.

When 0.5 c.c. of the plain toxoid used in this series was injected into a group of guinea pigs, it produced at the end of six weeks 0.1 unit of antitoxin per c.c. of pooled blood serum obtained from three animals. Injection of 1.0 c.c. produced a little more than 0.5 unit per c.c. of the pooled blood serum of four guinea pigs.

Our subjects showed 0.003 unit or less of antitoxin per c.c. of blood serum before active immunization was instituted. Eighteen to 32 days after the final dose was given all subjects but one showed 0.1 to 2.0 units of antitoxin per c.c. of blood serum. The exception (case 9963) showed 0.01 unit, but when tested 59 days after the third dose he had 0.25 unit. Two individuals dropped to less than 0.1 unit when retested 105 days after immunization. One of them (case 9972), when tested again three months later, showed 0.1 unit but dropped to less than 0.1 unit on subsequent tests. The same variation occurred in case 9963. This apparent discrepancy may be due to actual changes in the antitoxin content of the blood or to variation inherent to the biologic assay used. Of the subjects tested six months after immunization three persons or 27.3 per cent showed less than 0.1 unit. The rest had 0.1 unit or more. Three months later seven subjects, or 58.3 per cent of the tested individuals, had less than 0.1 unit. At the end of one year, two subjects showed 0.25 unit, while seven tested less than 0.1 unit.

* Received for publication February 28, 1939.

† We wish to thank Dr. E. A. Whitney, Medical Director of The Elwyn Training School, Elwyn, Pa., for allowing us to use inmates of this institution for this study. All antigens and tests reported in this paper were obtained from, and performed by, the Technical Division, Mulford Biological Laboratories, Sharp and Dohme, Glenolden, Pa.

CHART I
GROUP A

TETANUS TOXOID PLAIN 5969

Basic Course of Immunization: Three Doses 1.0 c.c. each.

Titer expressed in units of tetanus antitoxin per cubic centimeter of blood serum

Case	Control Titer	Interval Between 1st and 2nd Dose	Interval Between 2nd and 3rd Dose	Days After Third Dose Titer									
				32 days 0.50	91 days 0.25	182 days +0.25 -0.50	276 days +0.10 -0.25	370 days 0.25	461 days 0.25	657 days 0.10	748 days 0.1		
9960	0.003	31 days	28 days	32 days +1.0 -2.0	91 days +0.25 -1.0	182 days 0.25	276 days +0.10 -0.25	370 days +0.01 -0.10	461 days +0.01 -0.10	657 days 0.10	748 days 0.1		
9964	-0.003	31 days	28 days	32 days +1.0 -2.0	91 days +0.25 -1.0	182 days 0.25	276 days +0.10 -0.25	370 days +0.01 -0.10	461 days +0.01 -0.10	657 days 0.10	748 days 0.1		
9966*	-0.003	31 days	28 days	32 days 0.25	91 days 0.10	182 days +0.01 -0.10	276 days +0.01 -0.10	370 days +0.01 -0.10	461 days +0.01 -0.10	657 days 0.10	748 days 0.1		
9968*	-0.003	31 days	14 days	28 days 0.10	105 days +0.01 -0.10	196 days +0.01 -0.10	290 days +0.01 -0.10	384 days +0.01 -0.10	461 days +0.01 -0.10	657 days 0.10	748 days 0.1		
9972	-0.003	31 days	14 days	28 days 0.10	105 days +0.01 -0.10	196 days 0.10	290 days +0.01 -0.10	384 days +0.01 -0.10	461 days +0.01 -0.10	657 days 0.10	748 days 0.1		
9986*	-0.003	31 days	14 days	28 days 0.25	105 days +0.10 -0.25	196 days 0.10	290 days +0.01 -0.10	384 days +0.01 -0.10	461 days +0.01 -0.10	657 days 0.10	748 days 0.1		

* Received a "repeat injection."

CHART I—Continued

Case	Control Titer	Interval Between 1st and 2nd Dose	Interval Between 2nd and 3rd Dose	Days After Third Dose Titer							
				28 days +0.10 -0.25	105 days +0.10 -0.25	196 days +0.10 -0.25	290 days 0.10	384 days +0.01 -0.10	475 days +0.01 -0.10	—	—
9970	-0.003	31 days	14 days	27 days 0.01	59 days 0.25	105 days +0.01 -0.10	195 days 0.50	289 days 0.01	383 days +0.01 -0.10	—	—
9963*	-0.003	31 days	15 days	32 days 0.50	88 days 0.10	168 days —	262 days +0.01 -0.10	356 days +0.01 -0.10	—	—	—
9961	0.003	46 days	27 days	32 days 0.50	88 days 0.25	168 days +0.10 -0.25	272 days +0.10 -0.25	—	453 days 0.25	—	—
9969	-0.003	59 days	14 days	18 days +2.0 -3.0	88 days 0.50	168 days +0.25 -0.50	262 days 0.25	356 days 0.25	447 days +0.10 -0.25	643 days +0.10 -0.25	734 days 0.10
9967	-0.003	59 days	14 days	18 days 0.25	88 days 0.10	168 days +0.01 -0.10	262 days +0.01 -0.10	—	—	—	—

* Received a "repeat injection."

When retested 25 months after the basic course of immunization was completed, cases 9960 and 9969 still showed 0.10 unit per c.c. of blood serum.

Five members of this group A received a fourth or "repeat" dose of the same toxoid one year after the basic course of immunization had been completed (chart 2). At this time their antitoxin titer had fallen to $+0.01-0.1$ unit. When tested four days after the administration of the "repeat" dose, two subjects showed no change in titer, whereas three had increased to 0.1 unit or more. On the fifth day, all subjects showed good protection. The titer for the entire group ranged above 2.0 units per c.c. of blood serum one month after the stimulating dose was given. At the end of 16 months, there was a considerable drop in the antitoxin titer of the group, although it was still well above the minimum protective level of 0.1 unit.

A second group (B) of 12 young people received treatment similar to that given the members of Group A except that the antigen used consisted of the *tetanus toxoid plain* (No. 5969) to which 0.4 per cent alum had been added (chart 3).

The injection of 0.5 c.c. of this mixture of plain toxoid and of 0.4 per cent alum (No. 5969-5) into a group of eight standard guinea pigs resulted at the end of six weeks in the production of 2.0 units of antitoxin per c.c. of pooled blood serum. A similar titer was obtained following the injection of 1.0 c.c. of this antigen.

Before immunization, the control titer of our subjects was less than 0.003 unit. Eighteen to 46 days after the last dose of toxoid was given, all but one subject had more than 0.10 unit per c.c. of blood serum. The exception, case 9975, who had 0.10 unit, dropped to $+0.01-0.10$ unit when retested 104 days after the last dose of toxoid. When the group was retested 168 to 196 days after immunization, it was found that two additional individuals had dropped to -0.10 unit. Three months later another two subjects showed -0.10 unit, and at the end of one year six out of 10 patients tested showed -0.10 unit. The rest had 0.10 to 0.25 unit of antitoxin per c.c. of blood serum. When these four subjects were retested 22 months after the basic course of immunization was completed, one showed $+0.01-0.10$ unit while the other three had a good protective titer of 0.1 unit or more. Three months later, case 9981 dropped to -0.1 unit while two subjects, cases 9979 and 9976, showed $+0.10-0.25$ and 0.50 unit respectively.

Four members of this Group B received a fourth "repeat" dose of 1.0 c.c. of plain toxoid plus alum (No. 5969-5) one year after the basic course of immunization had been completed (chart 4). The control titer before the "repeat" injection was $+0.01-0.10$ unit. Four days later, only one subject showed 0.10 unit. The rest had -0.10 unit. On the fifth day, all but one subject had 0.10 to 0.25 unit. The exception still showed the control values of $+0.01-0.10$ unit. When retested on the seventh day, this subject had 1.0 unit. The entire group, with the exception of one

CHART II
GROUP A
TETANUS TOXOID PLAIN 5969
"Repeat" (Fourth) Dose (1.0 c.c.)

Titer expressed in units of tetanus antitoxin per c.c. of blood serum

Case	Days After 3rd Dose Titer	Interval Between 3rd and 4th Dose	Days After "Repeat" (Fourth) Dose Titer									
			4 Days	5 Days	7 Days	29 Days	91 Days	196 Days	287 Days	378 Days	474 Days	
9966	370 days +0.01 -0.10	370 days	+0.01 -0.10	0.10	+0.25 -0.50	+2.0 -3.5	1.0	+0.50 -1.0	0.50	0.50		
9963	383 days +0.01 -0.10	383 days	+0.01 -0.10	+0.10 -0.25	+1.0 -2.0	2.0	2.0	2.0	+0.50 -1.0	0.50	0.50	
9986	384 days +0.01 -0.10	384 days	+0.10 -0.25	+0.50 -1.0	3.5	+3.0 -5.0	+1.0 -3.0	+0.50 -0.75	+0.50 -0.75	0.25	+0.10 -0.25	
9968	384 days +0.01 -0.10	384 days	0.10	0.25	+1.0 -2.0	+3.0 -5.0	+1.0 -3.0	+0.50 -1.0	+0.50 -1.0	0.50	+0.25 -0.50	
9962	356 days +0.01 -0.10	356 days	0.10	0.25	+1.0 -3.0	+1.0 -3.0	+0.50 -1.0	+0.25 -0.50	+0.25 -0.50	+0.25 -0.50	0.25	

CHART III
GROUP B
TETANUS TOXOID PLUS ALUM 5969-5

Basic Course of Immunization: Three doses 1.0 c.c. each.
Titer expressed in units of tetanus antitoxin per cubic centimeter of blood serum

Case	Control Titer	Interval Between 1st and 2nd Dose	Interval Between 2nd and 3rd Dose	Days After Third Dose Titer							
				32 days +0.25 -1.0	88 days +0.25 -0.50	168 days +0.25 -0.50	—	—	—	—	—
9977	-0.003	46 days	27 days								
9983*	0.003	45 days	28 days	18 days 0.50	88 days 0.10	168 days +0.10 -0.25	262 days +0.01 -0.10	356 days +0.01 -0.10	—	—	—
9985*	-0.003	45 days	28 days	32 days 0.50	88 days 0.10	168 days +0.01 -0.10	262 days +0.01 -0.10	356 days +0.01 -0.10	—	—	—
9978*	-0.003	31 days	42 days	32 days 0.25	88 days +0.01 -0.10	168 days +0.01 -0.10	262 days +0.01 -0.10	356 days +0.01 -0.10	—	—	—
9979	-0.003	31 days	28 days	46 days +0.25 -1.0	91 days 0.25	182 days +0.10 -0.25	276 days +0.10 -0.25	370 days 0.10	461 days 0.10	566 days +0.10 -0.25	657 days +0.10 -0.25
9976	-0.003	31 days	28 days	32 days +1.0 -3.0	91 days +1.0 -2.0	182 days +0.5 -1.0	276 days +0.25 -0.50	370 days +0.25 -0.50	461 days +0.25 -0.50	566 days +0.25 -0.50	657 days +0.25 -0.50
										748 days +0.10 -0.25	748 days 0.50

* Received repeat (fourth) dose.

CHART III—Continued

Case	Control Titer	Interval Between 1st and 2nd Dose	Interval Between 2nd and 3rd Dose	46 days 0.25	91 days 0.10	182 days 0.10	276 days +0.01 -0.10	Days After Third Dose Titer	—	—	—	—	—
9974	-0.003	31 days	28 days	27 days 0.10	104 days +0.01 -0.10	195 days +0.01 -0.10	289 days +0.01 -0.10	383 days +0.01 -0.10	—	—	—	—	—
9975*	-0.003	31 days	15 days	27 days 0.10	104 days +0.01 -0.10	195 days +0.01 -0.10	289 days +0.01 -0.10	383 days +0.01 -0.10	—	—	—	—	—
9973	-0.003	31 days	15 days	27 days +0.10 -0.25	104 days +0.10 -0.25	195 days 0.10	289 days 0.10	383 days +0.01 -0.10	474 days +0.01 -0.10	—	—	—	—
9982	-0.003	31 days	14 days	28 days +0.25	105 days +0.25 -0.50	196 days +0.25 -0.50	290 days 0.10	384 days +0.01 -0.10	475 days +0.01 -0.10	—	—	—	—
9981	-0.003	31 days	14 days	28 days +0.25	105 days +0.25 -0.50	196 days 0.25	290 days +0.10 -0.25	384 days +0.10 -0.25	475 days 0.10	580 days 0.10	671 days 0.10	762 days +0.01 -0.10	—
9984	-0.003	31 days	14 days	32 days +0.25	105 days +0.25 -0.50	196 days +0.25 -0.50	290 days 0.25	384 days +0.10 -0.25	475 days +0.10 -0.25	580 days 0.10	671 days +0.01 -0.10	—	—

* Received repeat (fourth) dose.

CHART IV
GROUP B
TETANUS TOXOID PLUS ALUM 5969-5
"Repeat" (Fourth) Dose (1.0 c.c.)
Titer expressed in units of tetanus antitoxin per c.c. of blood serum

Case	Days After 3rd Dose Titer	Interval Between 3rd and 4th Dose	Days After "Repeat" (Fourth) Dose Titer									
			4 Days	5 Days	7 Days	29 Days	91 Days	196 Days	287 Days	378 Days	474 Days	
9975	383 days +0.01 -0.10	383 days	+0.01 -0.10	+0.10 -0.25	1.0	+0.5 -1.0	+0.25 -0.5	+0.25 -0.5	+0.10 -0.25	0.10	0.10	
9978	356 days +0.01 -0.10	356 days	+0.01 -0.10	0.25	3.0	+3.5 -5.0	+1.0 -3.0	0.75	0.25	0.25	+0.10 -0.25	
9985	356 days +0.01 -0.10	356 days	+0.01 -0.10	+0.01 -0.10	1.0	+1.0 -3.0	0.50	+0.25 -0.5	+0.10 -0.25	+0.10 -0.25	0.10	
9983	356 days +0.01 -0.10	356 days	0.10	+0.10 -0.25	+1.0 -2.0	2.0	+0.50 -1.0	1.0	0.50	0.50	+0.25 -0.50	

member, showed a further increase in the titer when retested 29 days after the repeat dose was given. At the end of three months, all the patients showed a drop in titer. However, the antitoxin content of the blood was still well above the minimum protective level of 0.1 unit per c.c. When retested 16 months after the "repeat" injection all four subjects showed 0.10 unit or more of tetanus antitoxin per c.c. of blood serum.

Eight young men (Group C) were immunized with two doses of *tetanus toxoid alum precipitated (refined)* (No. 8387-3). Half of the group received 0.5 c.c., whereas the other half got 1.0 c.c. at each injection. The two doses were given 146 days apart (chart 5).

When 0.5 c.c. of the toxoid used in this series was injected into a group of standard guinea pigs, there developed at the end of six weeks, five units of tetanus antitoxin per c.c. of pooled blood serum obtained from four animals. At the end of 12 weeks, two guinea pigs tested a little more than 3.0 units, whereas at the end of 25 weeks, tests on a surviving animal still showed a little more than 1.5 unit per c.c. of blood serum. The injection of a 1.0 c.c. dose of this alum toxoid produced at the end of six weeks 5.0 units of antitoxin per c.c. of pooled serum obtained from six guinea pigs. At the end of 12 weeks, the pooled serum of four pigs showed 9.0 units. At the end of 18 weeks the serum pooled from three animals showed 8.0 units, whereas at the end of 25 weeks after injection of the alum toxoid, one surviving guinea pig showed 4.0 units.

The control bleeding of our subjects before immunization showed — 0.003 unit of tetanus antitoxin. When tested 31 days after the second dose, all the members of the group had a good protective level of antitoxin titer in their blood, ranging from 0.25 to 7.0 units (chart 5). Little can be said concerning the effect of dosage upon the antitoxin titer in this small series of cases, since both the lowest and the highest values for the entire group occurred in those individuals that received the 0.5 c.c. dose. Two members of the 0.5 c.c. group showed the same titer as in the 1.0 c.c. group. When tested 90 days after the second injection of toxoid, one subject (case 10005), who on previous testing had shown the lowest value in the group, dropped to 0.01 unit. The rest still had a good protective titer. Two subjects that received the 1.0 c.c. dose also showed less than 0.10 unit when tested two months later. In other words, 43 per cent of the individuals tested five months after immunization was completed showed less than the amount of antitoxin necessary for protection. On the other hand, three members of the group showed 0.1 unit or more when tested 371 days after the second injection of toxoid. One of these subjects dropped to — 0.1 unit when retested 18 months after immunization. The other two subjects (cases 10006 and 10013) still showed 0.1 and 0.25 units respectively when tested about two years after the second dose of toxoid.

Three members of this group received a third or "repeat" injection of 1.0 c.c. of the same toxoid 237 days after the second dose, when the antitoxin level of their blood was less than 0.1 unit (chart 6). Four days after

CHART V
GROUP C
TETANUS TOXOID, ALUM PRECIPITATED, REFINED 8387-3
Two Doses Given 146 Days Apart.
Titer expressed in units of tetanus antitoxin per c.c. of blood serum

Case	Control Titer.	First Dose	Interval Between 1st and 2nd Dose	Second Dose	Days After Second Dose Titer								
					31 Days	90 Days	150 Days	237 Days	269 Days	371 Days	524 Days	615 Days	711 Days
10005*	-0.003	0.5 c.c.	146 days	0.5 c.c.	0.25	0.01	+0.01 -0.10	0.01	—	—	—	—	—
10006	-0.003	0.5 c.c.	146 days	0.5 c.c.	7.0	+1.0 -3.0	1.0	—	1.0	0.5	0.5	+0.25 -0.50	0.25
10011	0.003	0.5 c.c.	146 days	0.5 c.c.	0.75	—	—	—	—	—	—	—	—
10013	-0.003	0.5 c.c.	146 days	0.5 c.c.	3.0	+0.5 -1.0	+0.25 -0.50	—	—	0.25	0.10	0.10	0.10
10007	-0.003	1.0 c.c.	146 days	1.0 c.c.	+1.0 -2.0	0.50	0.25	—	0.10	0.10	+0.01 -0.10	—	—
10008*	0.003	1.0 c.c.	146 days	1.0 c.c.	+1.0 -3.0	+0.10 -0.25	+0.01 -0.10	0.01	—	—	—	—	—
10010	-0.003	1.0 c.c.	146 days	1.0 c.c.	3.0	+0.5 -1.0	0.50	—	0.25	—	—	—	—
10012*	-0.003	1.0 c.c.	146 days	1.0 c.c.	+0.5 -1.0	0.10	+0.01 -0.10	+0.01 -0.10	—	—	—	—	—

* Received a "repeat" (third dose).

CHARF VI
 GROUP C
 TETANUS TOXOID, ALUM PRECIPITATED, REFINED 8387-3
 Antitoxin Titer Following Injection of a "Repeat" (Third) 1.0 c.c. Dose.
 Titer expressed in units of tetanus antitoxin per c.c. of blood serum

Case	Titer Before Third Dose	Interval Between 2nd and 3rd Dose	Days After Third Dose Titer									
			4 Days	5 Days	6 Days	7 Days	29 Days	91 Days	196 Days	295 Days	386 Days	482 Days
10005	0.01	237 days	+0.01 -0.10	—	—	+1.0 -3.0	+1.0 -2.0	0.50	0.25	0.25	+0.10 -0.25	0.10
10008	0.01	237 days	+0.01 -0.10	—	+0.25 -0.50	+1.0 -2.0	1.0	+0.50 -1.0	0.25	+0.10 -0.25	0.10	0.10
10012	+0.01 -0.10	237 days	+0.01 -0.10	0.25	—	+1.0 -3.0	+3.0 -5.0	+1.0 -3.0	1.0	0.50	+0.25 -0.50	0.25

the "repeat" injection, they still showed less than 0.10 unit. On the fifth day, case 10012 had 0.25 unit. On the seventh day, all three subjects had more than 1.0 unit, an increase of over 100 per cent. A month after injection of the stimulating dose two subjects showed a decrease, whereas one member showed a considerable increase in the antitoxic titer of their blood. Good protection of 0.1 unit or more was still maintained 16 months later.

DISCUSSION

The injection of tetanus toxoid produces in most individuals a slight to moderate local reaction that lasts one to three days. No systemic reactions were encountered. The alum precipitated toxoid tends to produce a subcutaneous nodule at the site of injection similar to that produced by diphtheria alum toxoid. It is usually absorbed in two to four weeks.

The results obtained in the series of cases immunized with the plain toxoid compare favorably with those already reported in the literature.^{3, 4, 5, 7, 10, 11, 14} The subjects immunized with the plain toxoid plus 0.4 per cent alum, seemed to do a bit better than those injected with the plain antigen. However, the number of subjects is small and the differences noted are not clear cut enough to permit of any definite conclusions.

In agreement with Jones and Moss,¹⁴ we found that, within the limitations of the schedule (dose and time interval) used by us, two doses of alum precipitated toxoid produced a higher level of antitoxic immunity than three injections of plain toxoid or plain toxoid plus 0.4 per cent alum. The loss of antitoxin in all groups, regardless of the type of antigen used, was most marked in the first few months following the basic course of immunization, so that by the end of nine months to a year, the great majority of the immunized individuals showed less than the minimum protective level of 0.1 unit of antitoxin per c.c. of blood serum. Although the amount of antitoxin produced and lost varies in different individuals and is actually unpredictable, and though the loss in titer is not directly proportionate to the amount of antitoxin previously present in the blood, there is a definite tendency on the part of those subjects that develop the highest values of antitoxin to retain a protective titer for a longer period of time.

The first dose of alum precipitated toxoid affects the antitoxin producing cells of the body in such a manner that following a second injection there is a rather prompt increase in the antitoxin content of the blood. A certain period of time must elapse between these two injections before this release of antitoxin into the blood stream takes place. It may be as short as six weeks, and as long as five years and perhaps longer. The effect of the first dose of alum toxoid is rather unique in that it cannot be replaced by the natural occurrence of tetanus and recovery from it. We have had occasion to confirm Cowles'²¹ finding that a patient who had recovered from tetanus 10 years before still required two doses of alum toxoid before any demonstrable antitoxin appeared in the blood. Following the second dose, a few

days elapse before a protective titer develops. Hence, if an injury occurs during the interval between the two injections of alum toxoid and for a week or two following the second injection, passive immunization may be necessary in order to get full protection against tetanus.

The variability in the antitoxin response of different individuals following the primary series of injections, irrespective of antigen used, makes it necessary to administer a "repeat" or stimulating dose of toxoid whenever an injury occurs. Although the series of cases given a "repeat" dose of plain toxoid is small, there is a possibility suggested by our results that this plain antigen may be able to bring up the antitoxic content of the blood to the 0.1 unit level more quickly than is the case with the alum precipitated toxoid. This may be due to differences in absorption and deserves further study.

The "repeat" or stimulating dose of plain or alum precipitated toxoid produces within one week a remarkable increase in the antitoxin content of the blood. In most cases about five days elapse after the injection of the "repeat" dose before the antitoxin titer is brought up to or above the protective level. It is stated that the period of incubation of tetanus in man is usually from six to 14 days and is directly proportional to the amount of toxin and the severity of the disease. With a short period of incubation, six days or less, the disease is almost invariably fatal. Whether the mobilization of antitoxin that occurs after the injection of the "repeat" dose is fast enough to prevent all cases of acute tetanus is not definitely known, but more than likely it will be able to do so, since our minimum protective value of 0.1 unit is a conservative one. In this regard we must remember that we are dealing here with an active type of immunity that increases rapidly during the first four weeks after the "repeat" dose, when it reaches its highest level.

Between the first and third month after the "repeat" injection there is a sharp drop in antitoxin titer. Thereafter the loss is more gradual. Notwithstanding this, all subjects had a good protective titer when tested 16 months after the "repeat" dose. This is in marked contrast to the rapid antitoxin loss which these same subjects experienced after the primary course of injections, and would indicate that there is a greater permanency in the protective titer that develops after injection of the stimulating dose. This finding is in agreement with similar observations made by Jones and Moss.⁸¹

From our studies to date, it would appear that active immunization against tetanus by means of the injection of two doses of alum precipitated toxoid followed by a "repeat" injection upon the occurrence of an injury, will prove to be of value in military practice, in civil life where frequent injuries make the repeated injection of tetanus antitoxin impossible, and in the handling of allergic individuals who are sensitive to horse serum.

CONCLUSIONS

1. Two injections of tetanus alum precipitated toxoid produce a higher antitoxin titer than three injections of plain toxoid, when given in accordance with the schedule used in this study.

2. Following the basic course of immunization there is a rapid and variable loss of antitoxic immunity. This necessitates the injection of a "repeat" or stimulating dose of toxoid at the time of injury.

3. The "repeat" dose will bring up the antitoxin level of the blood of a previously immunized subject to a protective level of 0.1 unit or more within four to six days.

4. One week after the "repeat" dose, the antitoxin titer of an immunized subject is from two to 50 times greater than the titer produced by the injection of 1,500 units of tetanus antitoxin.

5. Following the "repeat" injection of toxoid, the protective titer seems to be maintained for a longer period of time than is the case after the basic course of immunization.

REFERENCES

1. DESCOMBEY, P.: Tetanus anatoxin, *Compt.-rend. Soc. de biol.*, 1924, xci, 239.
2. RAMON, G., and ZOELLER, C.: Tetanus anatoxin and active immunization of humans against tetanus, *Ann. Inst. Pasteur*, 1927, xli, 805.
3. RAMON, G., and ZOELLER, C.: New results concerning human vaccination against tetanus, *Compt.-rend. Soc. de biol.*, 1929, c, 92.
4. RAMON, G., and ZOELLER, C.: On the value and duration of immunity conferred on humans by vaccination with tetanus antitoxin, *Compt.-rend. Soc. de biol.*, 1933, cxii, 347.
5. SACQUEPEÉ, E.: Immunization against tetanus, *Paris méd.*, 1933, i, 491.
6. LINCOLN, E. M., and GREENWALD, C. K.: Active immunization of human beings with tetanus toxoid, *Proc. Soc. Exper. Biol. and Med.*, 1933, xxx, 1241.
7. SNEATH, P. A. T.: Development of tetanus antitoxin following administration of tetanus toxoid, *Jr. Am. Med. Assoc.*, 1934, cii, 1288.
8. BERGEY, D. H.: Active immunization against tetanus infection with tetanus toxoid, *Jr. Infect. Dis.*, 1934, lv, 72.
9. BERGEY, D. H., and ETRIS, S.: Immunization of humans with alum precipitated tetanus toxoid, *Am. Jr. Pub. Health*, 1934, xxiv, 582.
10. SNEATH, P. A. T., and KERSLAKE, E. G.: Further observations following administration of tetanus toxoid, *Canad. Med. Assoc. Jr.*, 1935, xxxii, 132.
11. SNEATH, P. A. T., and KERSLAKE, E. G.: Persistence of tetanus antitoxin in man following active immunization, *Brit. Med. Jr.*, 1935, ii, 290.
12. RAMON, G.: The diphtheria, tetanus and staphylococcus anatoxins, and their application, *Ext. de L'Echo méd. du nord, Numéro Spécial du May 31*, 1936.
13. RAMON, G.: Tetanus anatoxin and the prevention of tetanus in man and domestic animals, *Cong. Internat. de Microbiol. Londres*, 1936.
14. JONES, F. G., and MOSS, J. M.: Studies on tetanus toxoid. Antitoxic titer of human subjects following immunization with tetanus toxoid and tetanus alum precipitated toxoid, *Jr. Immunol.*, 1936, xxx, 115.
15. BERGEY, D. H., and ETRIS, S.: Active immunization against tetanus infection with refined tetanus toxoid, *Jr. Immunol.*, 1936, xxxi, 363.
16. BERGEY, D. H., and ETRIS, S.: Tetanus toxoid, *Clin. Med. and Surg.*, 1936, xliii, 30.

17. GOLD, H.: Studies on tetanus toxoid. I. Active immunization of allergic individuals with tetanus toxoid, alum precipitated, refined, *Jr. Allergy*, 1937, viii, 230.
18. GOLD, H.: Studies on tetanus toxoid. II. Active immunization of normal persons with tetanus toxoid, alum precipitated refined, *Jr. Am. Med. Assoc.*, 1937, cix, 486.
19. HALL, W. W.: Active immunization against tetanus with tetanus toxoid, *Mil. Surgeon*, 1937, lxxx, 104.
20. MCBRYDE, A.: Tetanus immunization with alum precipitated toxoid, *South. Med. Jr.*, 1937, xxx, 565.
21. COWLES, P. B.: Tetanus immunization, *Yale Jr. Biol. and Med.*, 1937, ix, 409.
22. JONES, F. G., and MOSS, J. M.: Studies on tetanus toxoid. II. The response of human subjects to an injection of tetanus toxoid or tetanus alum precipitated toxoid one year after immunization, *Jr. Immunol.*, 1937, xxxiii, 183.
23. JONES, F. G., and MOSS, J. M.: The antitoxic titers of human subjects following immunization with combined diphtheria and tetanus toxoids, alum precipitated, *Jr. Immunol.*, 1937, xxxiii, 173.
24. RAMON, G.: Tetanus toxoid and its use and value in immunization, *Ann. de méd.*, 1937, xlii, 358.
25. RAMON, G.: Tetanus immunity and influence of injections of stimulating adjuvant substances mixed with antigen, *Rev. d'Immunol.*, 1937, iii, 193.
26. GOLD, H.: Active immunization of allergic individuals against tetanus by means of tetanus toxoid, alum precipitated, refined, *Jr. Allergy*, 1938, ix, 545.
27. GOLD, H.: Active immunization against tetanus by means of tetanus toxoid, alum precipitated, refined, *Jr. Lab. and Clin. Med.*, 1938, xxiii, 903.
28. HAYDEN, R., and HALL, W. W.: Active immunization against tetanus using alum precipitated toxoid, *U. S. Nav. Med. Bull.*, 1938, xxxvi, 524.
29. BOYD, J. S. K.: Active immunization against tetanus, *Jr. Roy. Army Med. Corps*, 1938, lxx, 289.
30. SACQUEFEE, E., PILOD, M., and JUDE, A.: Antidiphtheric and antitetanic immunity in adults after associated triple revaccination against typho-paratyphoid fever, diphtheria and tetanus, *Rev. d'Immunol.*, 1938, iv, 389.
31. JONES, F. G., and MOSS, J. M.: Combined diphtheria toxoid and tetanus toxoid, alum precipitated, *Jr. Lab. and Clin. Med.*, 1939, xxiv, 512.
32. GOLD, H.: On the value of a "repeat" injection of tetanus toxoid (secondary stimulus) in active immunization against tetanus, *Jr. Lab. and Clin. Med.* (to be published).

THE EFFECT OF ROENTGEN-RAY ON THE BLOOD CODEHYDROGENASES I AND II*

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It is a well known fact that therapeutic doses of roentgen-ray frequently give rise to a train of symptoms characterized by nausea, vomiting, abdominal cramps, headache and general malaise. The name "roentgen sickness" has been applied to this syndrome. Many remedies for this condition have been used with varying but often favorable results. One of the first used was parenteral liver extract.¹ More recently, thiamin hydrochloride, ascorbic acid and nicotinic acid, all of which affect cellular oxidation and reduction, have proved efficacious in the therapy of many cases.^{2, 3, 4} Because of these associations, the authors thought that a disturbance of the cellular respiratory processes by roentgen-ray might explain the pathogenesis of roentgen sickness. The codehydrogenases I and II (co-enzymes), which contain the amide of nicotinic acid, appear to be catalysts of universal importance in the biological oxidations of the cell. We have therefore investigated the quantitative variation in these blood co-enzymes in patients both before and after exposure to roentgen-ray therapy.

MATERIAL AND METHOD

Eight patients were selected for study, and observations were made during a series of from one to four roentgen-ray exposures in each case. Three individuals recuperating in the hospital following herniorrhaphy and two patients with myelogenous leukemia received roentgen-ray over the spleen. Two of these cases were given 500 milligrams of nicotinic acid just before irradiation. Two pellagrins in remission, one of whom was maintained on 500 milligrams of nicotinic acid per day, were hospitalized and received roentgen-ray over the spleen. Another pellagrin in remission remained ambulatory and received roentgen-ray over the ear for the control of a basal cell carcinoma.

Repeated determinations of the blood codehydrogenases I and II were made on samples of venous blood according to the method described previously.^{5, 6} Roentgen-ray was administered in courses of 200 r units (distance of 15", milli amps 5, filters 1 mm. copper and 1 mm. aluminum, time of exposure 33 minutes),† and the amount of codehydrogenases I and II

* Received for publication July 25, 1939.

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† Two of the patients were treated at the Cincinnati General Hospital, and received roentgen-ray in courses of 200 r units (200 kilovolts, 15 milli amps, distance of 50 centimeters T. S. D., filter 1 thoreus, time of exposure 13½ minutes).

present in the blood was determined at intervals of 6, 12, 18, 24, 48, and 72 hours following radiation. Five hundred determinations on the blood of normal persons and patients with organic diseases served as controls.

Previous studies have shown that following roentgen-ray therapy, ether-soluble pigments which have the color of porphyrin in 25 per cent hydrochloric acid, and which are similar to those found in the urine of pellagrins in relapse, are excreted in the urine.⁴ The urine of each person who received roentgen-ray, therefore, was tested for these substances before and after radiation.

RESULTS

The representative graph, figure 1, illustrates the typical findings in one of the eight cases studied. In those cases which received no nicotinic acid the concentration of the cohydrogenases I and II in the blood de-

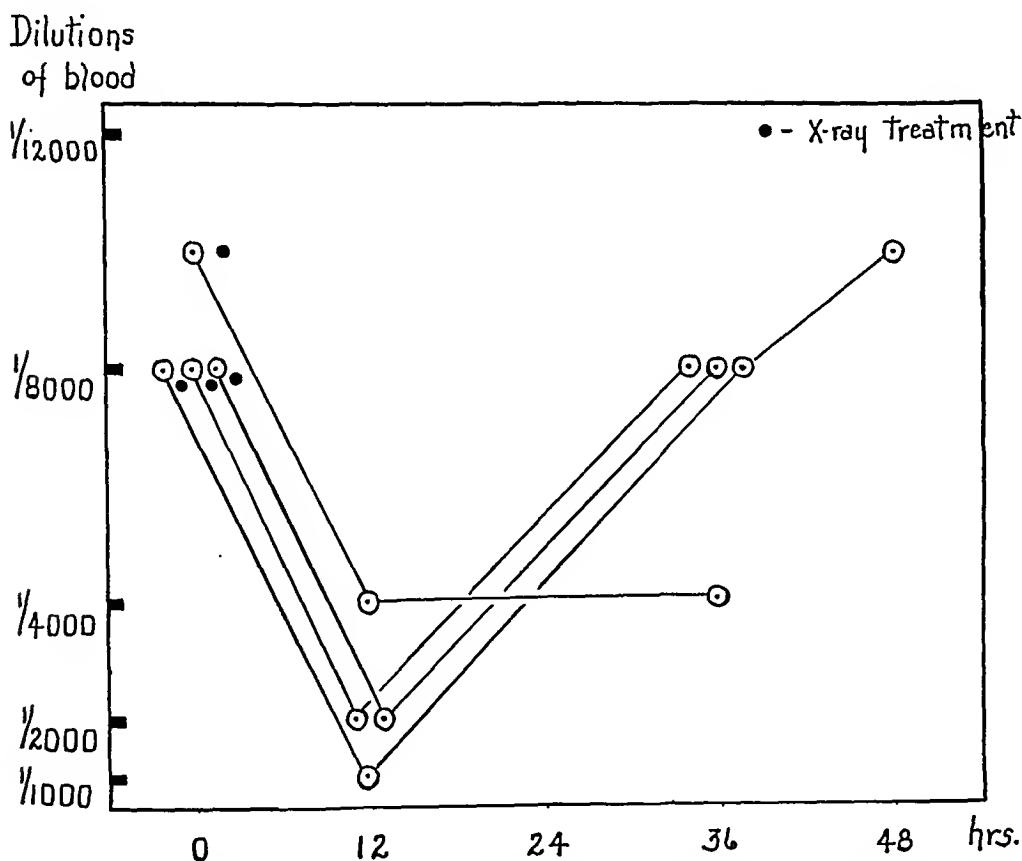


FIG. 1. Four studies of the effect of roentgen-ray treatment on the co-enzymes I and II in the blood of a pellagrins in remission as shown by the growth of *B. influenzae*.

creased 60 to 90 per cent within six to 12 hours after radiation, and then gradually increased so that after 24 hours the initial concentration was reached. On the second, third, and fourth days following roentgen-ray, the concentration of these co-enzymes remained constant. In contrast, none of

the controls showed such extraordinary and sudden decreases in the co-enzyme concentration as were observed in the persons who received roentgen-ray radiation. The pellagrin in remission who received 500 milligrams of nicotinic acid daily for two weeks did not develop roentgen sickness during a course of three roentgen-ray exposures, but after each exposure the co-enzyme concentration in the blood decreased slowly to 50 per cent of the original values. In the two persons to whom a single dose of 500 milligrams of nicotinic acid was administered just before radiation, the co-enzyme concentration decreased, but in neither case was the patient nauseated nor was there an increase in the excretion of pigments in the urine.* In all other cases, however, these pigments appeared in the urine 12 hours after radiation and disappeared within 48 hours.

SUMMARY AND CONCLUSIONS

1. Determinations of codehydrogenases I and II were made before and after roentgen-ray radiation on the blood of three healthy persons, two cases of myelogenous leukemia, and three pellagrins in remission.

2. Ether-soluble pigments which have the color of porphyrin in 25 per cent hydrochloric acid, similar in appearance to those found in the urine of pellagrins, appeared in the urine of these patients 12 hours after radiation and disappeared within 48 hours.

3. Nicotinic acid, administered before radiation, prevented the excretion of abnormal pigments but did not prevent the decrease in the co-enzyme content of the blood.

4. In those cases which received no nicotinic acid, the blood codehydrogenases I and II concentrations invariably decreased 60 to 90 per cent within 12 hours following exposure to roentgen-ray, and gradually returned to their former level at the end of 24 hours.

5. The results of this study, and the frequently reported beneficial effect of nicotinic acid and other vitamins in the treatment of "roentgen sickness" suggest that a number of cellular oxidation-reduction enzyme systems may be affected by exposure to roentgen-ray.

BIBLIOGRAPHY

1. YOUNG, B. K.: Liver extract as a remedy for roentgen sickness, *Am. Jr. Roentgenol.*, 1936, xxxv, 681.
2. MARTIN, C. L., and MOURSUND, W. H., JR.: Irradiation sickness, *Radiology*, 1938, xxx, 277.
3. CARRIE, C.: Value of vitamin C for prevention of leukopenia due to irradiation, *Klin. Wchnschr.*, 1938, xvii, 163.
4. SPIES, T. D., and BEAN, W. B.: The rôle of nicotinic acid in the prevention of pellagra, roentgen sickness and increased porphyrinuria, *Jr. Clin. Invest.*, 1938, xvii, 504 (abstract).

* The effects of yeast and wheat germ are being studied in a similar manner.

5. VILTER, R. W., VILTER, S. P., and SPIES, T. D.: Relationship between nicotinic acid and a codehydrogenase (cozymase) in blood of pellagrins and normal persons, Jr. Am. Med. Assoc., 1939, cxii, 420.
6. VILTER, R. W., VILTER, S. P., and SPIES, T. D.: Determination of the codehydrogenases I and II (cozymase) in the blood of diabetics in severe acidosis, Am. Jr. Med. Sci., 1939, cxcvii, 322.
7. VILTER, R. W., VILTER, S. P., and SPIES, T. D.: A note on the blood codehydrogenases I and II in lymphatic or myelogenous leukemia, South. Med. Jr., 1939, xxxii, 619.

THE USE OF DILANTIN IN THE TREATMENT OF EPILEPSY *

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THE drug diphenyl-hydantoin has been known for several years but it was so nearly insoluble that it was considered practically useless. In 1937 the sodium salt of this compound was prepared in the Parke-Davis Laboratories and this drug (sodium-diphenyl-hydantoinate) was studied for anticonvulsant properties by Merritt and Putnum of Boston.¹ Because of its promise as an anticonvulsant, thorough pharmacological studies were made. Animal experimentation showed it to be practically non-toxic and to have little or no hypnotic effect. The method of excretion and end products could not be determined. From observation it was believed that there was no tendency toward storage and that it was entirely eliminated from the body within 48 hours, but in what form and by what route was unknown.

After a year's clinical use and careful animal studies, the drug was offered to us for clinical use in the Epilepsy Clinic in Detroit. During January 1938, 50 children were started on this treatment, all of whom had been under observation for months and, in many instances, for two and three years. A period of observation free from other drugs was made in all cases except those having frequent hard seizures where such procedure would obviously have been a hardship, if not a real danger.

In this paper only our clinical experience with Dilantin (sodium-diphenyl-hydantoinate) over the past 15 months will be given. A general discussion of epilepsy is not intended.

The effectiveness of Dilantin in the control of seizures has been greater than we expected. This series of cases includes 220 children and young adults, most of whom have taken Dilantin for six months or longer. Fifty have taken this drug continuously for over a year. With few exceptions, the age level is from six to 20 years, the greater number of cases being in the second decade.

In a clinical study of epilepsy the very nature of the disease precludes a satisfactory statistical report because of the many variables. The type of seizure varies from the most fleeting *petitmal* to a *status epilepticus*; the frequency may be one seizure a year in one case and in the next case, six seizures a day; the etiological factors may vary from a severe brain injury to a truly idiopathic type. Again there is the special variation associated or confused with chorea; or the more subtle variety sometimes called "epileptic equivalents" with moments of excitement and temper: Foster Kennedy's "endogenous emotional tempests."

* Received for publication May 11, 1939.

Apart from the influence on convulsions, there are other benefits from the use of Dilantin. There is a marked change in mental state and personality. This change is more noticeable if strong sedatives have been previously used. There is a definite improvement in memory and concentration. A sense of composure and sureness, with a return of social interest is evidenced within a few weeks. All of these benefits are real but hard to tabulate. In a broad way the results from the use of Dilantin may be summarized as follows:

In 55 per cent of the cases the seizures are entirely controlled.

In another 20 per cent the seizures are modified or partially controlled.

In 25 per cent there is little or no improvement.

The untoward effects can be listed as: (1) acute toxic conditions such as a skin rash or manifestations of toxic damage of the nervous system; (2) conditions suggestive of chronic irritation, coming on after two or three months' continuous use of Dilantin and gradually increasing with the continued use of the drug. Here are included sore mouth with an unusual hyperplasia of the gums, and frequently associated with these changes are repeated attacks of gastrointestinal irritability.

More specifically, in approximately 10 per cent of the cases a skin rash appears during the second week. This rash closely resembles measles, and there may be an increase in temperature to 101 degrees, and bronchial irritation. Usually, after omitting the drug for two days, treatment can be resumed. Symptoms of central nervous system intoxication are dizziness, confusion, an unsteady swaying gait, weakness, ataxia, and, in a few instances, a mild psychosis.

The most serious complications have been the unusual gum-changes and the repeated attacks of gastric irritation. The gastric upset has been seen only in cases showing the hyperplasia of the gums. They appear to be inter-related and in some way concerned with a deficiency of vitamin C. The gingival hyperplasia was first observed in June 1938, but the etiology was not known. By August, several such cases with the same history had been seen. All were on Dilantin and had complained of sore mouth two to four weeks after starting this treatment. The soreness had disappeared in about two weeks but was followed by a swelling of the gums. Fifty-one per cent of all our cases, who have been on Dilantin three months or more, show these gum changes to some extent. Our observations of these gum changes up to December 1, 1938, were recently published in the *Journal of the American Medical Association*.²

One important observation has been made since that paper was written, that is, that these markedly hyperplastic gums return gradually and entirely to normal within three months when the drug is discontinued, although the diet remains the same and no additional vitamin C is supplied. One girl, aged 14, had a severe hyperplasia of the gums with bleeding and soreness



FIG. 1. This photograph of the mouth of a 10-year old girl shows only the points of the teeth above the hyperplastic gum. This photograph was taken February 21, and by March 23 the teeth were entirely covered over.

last fall. She was one of those designated as a three plus hyperplasia in the study which was reported recently. At that time her blood serum ascorbic acid was 0.12 mg. per 100 c.c. of blood. At the request of her mother Dilantin was discontinued December 1. She had no cevitamic acid and her diet was of only average or below average concentration of vitamin C. By

March 23 her gums were perfectly normal again and the blood serum ascorbic acid was 0.85 mg. per 100 c.c. of blood. The results of further study of the blood serum ascorbic acid parallel the findings reported in the recent article, namely: the decrease in ascorbic acid appears to be proportional to the severity of the hyperplasia.

On two separate cases biopsy of the hypertrophied gums has been made. Each shows microscopically a marked proliferation of the mucous membrane and connective tissue. It has the appearance of a chronic irritation and not of an infection.

Soon after our school clinic opened last autumn, we began to see attacks of acute gastric irritation, all of which were similar in history and symptoms. These cases suffered considerable pain and soreness in the epigastrium, severe nausea and vomiting and complete anorexia. Each case lasted about 48 hours. It was observed that all had been on Dilantin two months or more, and all had hyperplasia of the gums. It was found that such attacks of acute gastrointestinal upset had been occurring since April and May. Unfortunately, most of these first attacks occurred at home. Several were referred to the hospital and in two instances a diagnosis of acute appendicitis was made, immediate operation advised and performed, and in each case there were subsequent similar attacks. The temperature is always normal or below and there is no rigidity of abdominal muscles nor increase of leukocytes.

During this period a detailed study was made in one case: a young man, 19 years of age, residing in Cleveland, where circumstances permitted hospitalization whenever needed. This is the same case reported in our recent article. The relation of the gum changes, the gastrointestinal symptoms and the blood serum ascorbic acid were carefully investigated. From August 15 to September 15, the patient had received 300 mg. cevitic acid dissolved in lemon juice daily in addition to a diet high in vitamin C. From September 15 to October 22, the excess vitamin C (cevitic acid) was omitted but a high vitamin C diet continued. On October 22 his blood serum ascorbic acid was 0.1 mg. per 100 c.c. of blood. From October 22 to November 22, he was again given 300 mg. of cevitic acid daily in addition to a high vitamin C diet. On November 22, his blood serum ascorbic acid was 1.8 mg. per 100 c.c. of blood. He appeared in excellent health and was stronger and happier than he had been before. At this point all citrus fruits, as well as the excess vitamin C, were eliminated. In addition to a well balanced diet he had one glass of tomato juice daily. On December 12, he developed an attack of extreme nausea, vomiting and pain in the epigastrium which lasted three days. On December 15, he was seen and referred to the hospital. At this time, his blood serum ascorbic acid was below 0.1 mg. per 100 c.c. of blood. The gums had become spongy and purplish-red and bled easily on slight pressure. For several days previous to the attack of vomiting he complained of weakness and a loss of muscular control. On December 18, gastroscopy showed no ulcers, normal motility and essentially



FIG. 2. Microscopic photograph of gum.

normal rugal folds of the stomach. There was a question of hypertrophy and increased redness of the rugal folds but it was not sufficiently pronounced to permit of a definite statement. On the posterior wall of the stomach there was a discolored area one inch in diameter which had been caused by a recent submucosal hemorrhage.

This gastroscopic study was made because of an unfavorable result in a similar case in Detroit. A young man above school age, who had previously been one of our students and was known to us, was taking Dilantin on our advice but under the direction of his private physician. He had taken Dilantin, 0.4 gm. daily, from July to the middle of November and his seizures had been entirely controlled. According to the history given us he suddenly developed nausea, vomiting, pain in the epigastrium, and anorexia. On the third day of his illness, although greatly improved, he had a very slight seizure because he had not been able to take Dilantin. He was up and around and was anticipating lunch, at which time he was to resume the treatment, when suddenly he started to cough and to vomit blood. This hemorrhage continued, proving fatal before the physician could arrive.

From these two cases we get a clinical picture of gastritis with hemorrhage, a condition similar to, and in some way connected with the gum changes. It appears that both of these conditions are in some way related to deficiency of vitamin C. In all, 62 attacks of gastrointestinal disturbance were observed. Since December this condition has been prevented, with few exceptions, by giving the children excess amounts of vitamin C. All are on a diet high in vitamin C and those showing gum changes are given cevitamic acid in addition to citrous fruits.

As stated above, Dilantin is the most powerful anticonvulsant thus far used. It is equally effective in the control of seizures in cases with brain injury as in the so-called "idiopathic" type. The action is so definite that in severe cases the seizures may be controlled the first day. There is no cumulative effect and the drug is eliminated within two or three days. There is no mental depression or hypnosis such as seen with heavy doses of phenobarbital and some of the commonly used patent medicines. Usually, where the seizures are entirely controlled, the amount can be reduced safely after about six months. The results have been so definite that we occasionally employ Dilantin as a diagnostic test in questionable cases of so-called "epileptic equivalents."

On Dilantin there is a definite improvement in mental faculties and emotional stability. In general, if there is no associated brain injury or mental deficiency, there is a tendency to return to normal in every way. The majority of children can receive this treatment continuously for months under careful medical supervision.

This paper was read before the Detroit Academy of Medicine, April 10, 1939, and this summary is our continued study of the same group to August 1, 1939. During April and May we saw no cases of upset and for a time thought that we had finally controlled this condition and that our experience

as related in this paper would never be repeated. However, during June and July five different cases under my observation developed attacks of severe gastric upset. One girl on two different occasions, once in June and again in July, was sent to the hospital with the diagnosis of appendicitis for operation. The absence of fever, abdominal rigidity and leukocytosis held up the operation each time. In this case the gums showed marked hyperplasia, sponginess with bleeding and soreness. No blood serum ascorbic acid determination or gastroscopic study was made. These five cases were all on a diet high in vitamin C, but none was taking extra vitamin as cevitamic acid.

We have no satisfactory explanation for this variation in number of cases of gastric irritation seen during this past year. Whether there is naturally a low intake of vitamin C during the fall and winter months, or whether we brought about an abnormally high vitamin C intake during the spring months by our insistence on such a diet can not be determined. Possibly there is some other factor.

To date we are unable to prevent all of the cases of acute gastric distress, but will continue the use of Dilantin with even more emphasis on a high vitamin C diet and with a recheck each month for symptoms suggesting the onset of these toxic phenomena.

REFERENCES

1. MERRITT, H. H., and PUTNUM, T. J.: Sodium diphenyl-hydantoinate in the treatment of convulsive disorders, *Jr. Am. Med. Assoc.*, 1938, cxi, 1068.
2. KIMBALL, O. P.: The treatment of epilepsy with sodium diphenyl-hydantoinate, *Jr. Am. Med. Assoc.*, 1939, cxii, 1244.

SOME STUDIES IN THE MECHANISM OF CARDIAC HYPERTROPHY *

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HYPERTROPHY of the heart is a reliable sign of heart disease. A definitely enlarged heart is foredoomed to failure. The functional disadvantages of enlargement of the myocardial fibers have been stressed by Harrison, Ashman, et al.¹ and by Wearn, Roberts, et al.² Cardiologists have held that recognizable hypertrophy is always pathological, progressive, irreversible and eventually detrimental. The argument that heart muscle hypertrophy may be advantageous like that of skeletal muscle, as exemplified by the blacksmith's biceps, may be countered with the argument that Sandow was really muscle-bound. The bulging muscle makes a striking show; but the long sleek muscle strikes the sharper blow.

The not infrequent case of chronic hypertension without cardiac enlargement and the question of the reversible heart have intrigued us. There have been opinions voiced recently that hypertrophy may be curtailed and that it may actually be reversible. Christian³ advocated the use of digitalis to restrain hypertrophy on the basis of Cloetta's observations.⁴ Matas and Heninger⁵ have recently emphasized the disappearance of hypertrophy upon closure of an A-V aneurysm. Such facts have excited the interest of clinicians, as well as pathologists, in the processes concerned in myocardial overdevelopment. The clinician wants to know what factors contribute to pathological cardiac hypertrophy and what steps might be taken to curtail or reverse the processes. This calls for consideration of clinical and experimental data.

Normal hearts do not hypertrophy in the clinical and pathological sense as a result of physical activity, exercise, training, competitive athletics and feats of strength and endurance. These must put some strain upon the heart, but in practically all studies of athletes, with the exception of those of Tung et al.⁶ on ricksha-pullers, no recognizable enlargement has been found. Some compensatory chemical, physiological and histological changes must result from strenuous preparatory efforts, yet in most athletes our inadequate clinical methods fail to reveal any changes. The point at which physiological strengthening ends and pathological hypertrophy begins is difficult of establishment. Clinically a heart with its point of maximum apex impulse inside the nipple line we accept as normal, and must consider as ab-

* Read at the New Orleans meeting of the American College of Physicians March 28, 1939.

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Aided by Grants Nos. 444 and 530 of the Committee on Scientific Research of the American Medical Association.

normal any detectable displacement of the point of maximum impulse of the heart's apex or extension of the borders of the heart beyond the left mid-clavicular line or the right sternal border. These signs indicate cardiac enlargement which, even though largely dilatation, still spells heart disease. The diagnosis of cardiac hypertrophy should be reserved and questioned until actually increased weights have been obtained, or the ventricular thickness has been demonstrated by Robb's method.⁷

Work hypertrophy apparently is compensatory and aids in the maintenance of circulatory equilibrium in progressive hypertensive arteriolar disease, chronic cardiac valvular disease, and mediastinal or parietal anchorage of an adherent pericardium. But in all of these there are, in addition to the added work, other factors such as progressive arteriolar changes, inflammatory reactions, with scar tissue or coronary artery constriction. As the demands persist, the damaged human heart overdoes matters and responds to injury and the extra burden with pathological cardiac hypertrophy. The mechanism of production of pathological cardiac enlargement as well as the adequacy and efficiency of such hearts, are still open questions. There is more than a little doubt that it is a response to the added work stimulus or dilatation alone. It is an interesting fact that by no means of experimentation thus far have we been able to produce any extreme grade of cardiac hypertrophy in animals comparable to that seen in humans.

The enlargement of the heart in *arteriovenous aneurysm* is 90 per cent to 75 per cent dilatation, and all but 10 per cent to 25 per cent will be removed by closure of the fistula. The longer the A-V communication remains open, the more genuine hypertrophy develops and the less likely is complete reversibility possible.

The cardiac enlargement occasionally found in the *myxedematous* patient is not cardiac hypertrophy in the restricted sense; pathologically, physiologically and chemically it differs from that of hypertensive disease. It is the result of a metabolic disorder of the heart muscle, as of all tissues, with an increased retention of water. It disappears under the stimulus of thyroid extract medication.

The *beri-beri* heart is likewise not a true myocardial hypertrophy but a disturbance in the cardiac cellular metabolism that weakens the myocardium and leads to increase in the size of the heart. The enlargement vanishes with the building up of the vitamin B content of the body.

The fact that the clinician accepts cardiac hypertrophy as a pathological process creates the stimulus for the studies directed toward determination of the causes and the methods for the prevention of this over-compensatory development. A consideration of the main theories that have been propounded in explanation of cardiac hypertrophy is in order in the beginning of a discussion of the subject.

SOME THEORIES OF THE MECHANISM OF CARDIAC HYPERTROPHY

The many theories of hypertrophy of the heart are exhaustively discussed by Mönckeberg.⁸ We present a skeleton abstract of Mönckeberg's survey, with some additions from the recent literature.

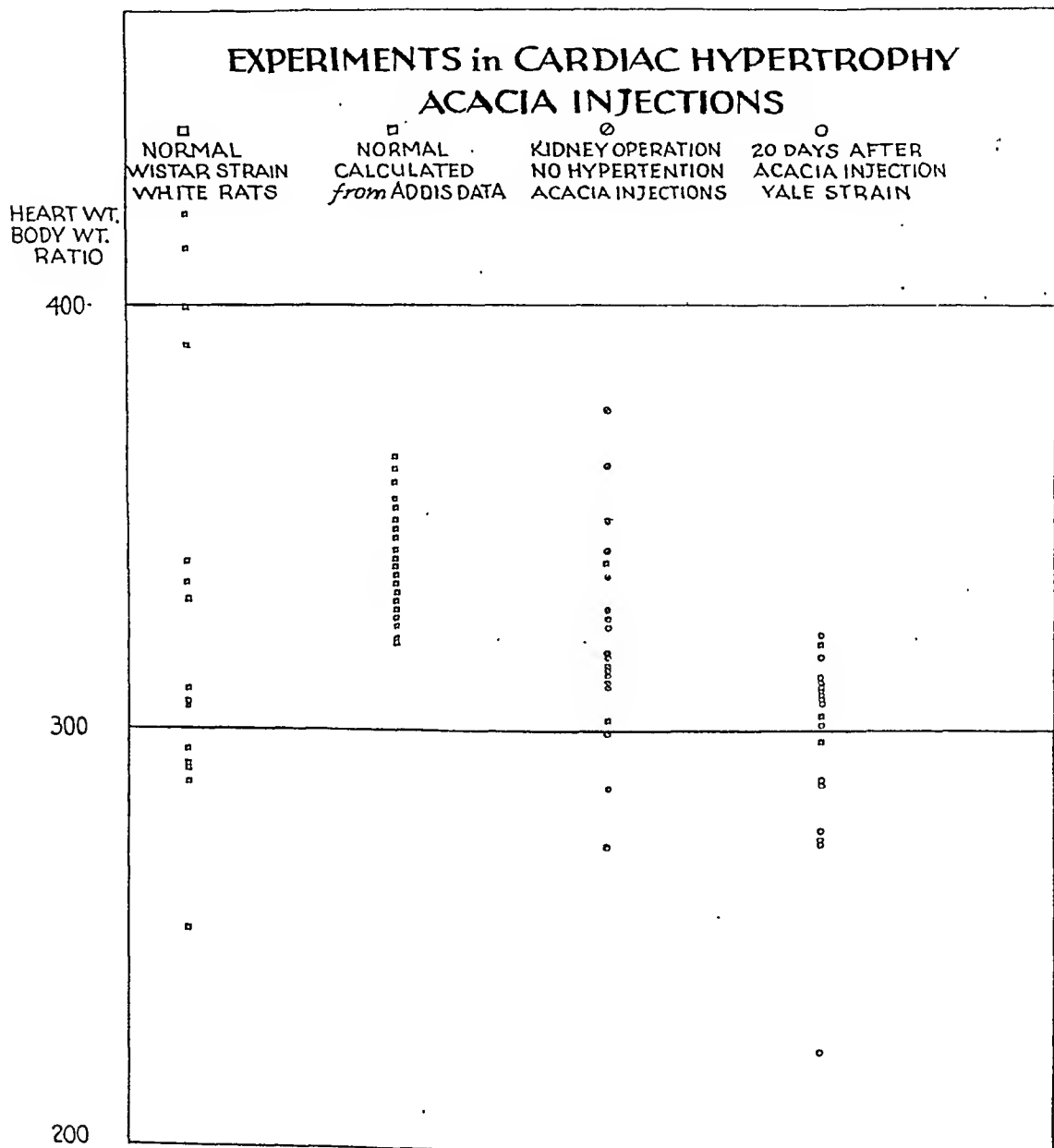
The pure work hypothesis of cardiac hypertrophy was advanced by Cohnheim who observed that the heart chamber that was called upon to bear an extra burden showed cardiac hypertrophy. Cohnheim stated that aside from extra work there was no other physiological pathological moment that could cause muscle to develop beyond its normal growth level. He insisted that when there was an increase in the number or thickness of the myocardial cells or fibers one could conclude absolutely that the muscle had been called upon to do more than its normal amount of work over a long period of time. Thorel maintained that in spite of muscular exertion the normal heart does not develop hypertrophy. Most of the older pathologists agreed that the normal heart would increase somewhat in size under the stimulus of exercise. However, it was not clearly established when strengthening of the normal heart stopped and work hypertrophy as a pathological process began.

Rothberger taught that the heart might enlarge from other causes, perhaps as a result of increased supply of nourishment. Rosenbach pointed out that increased nourishment was merely part and parcel of the reaction to effort, with increased coronary flow merely a response to the demand. Koester suggested that the increased length of the diastasis period was all-important, inasmuch as there was a compression of the coronary vascular bed during systole, with resulting ischemia of the heart muscle. In complete diastole, too, there is such stretching of the coronary vascular bed that the intramural circulation is embarrassed during this phase. Hence the importance of diastasis, the period between the two extreme phases when the greatest flushing of the coronary blood, with its nutritional material, takes place. Prolongation of the period of diastasis may therefore lead to greater assimilation and hypertrophy.

Letulle, Rindfleisch and Orth came to the conclusion, upon the basis of histological studies, that in hypertrophy there was multiplication of the cells or splitting of fibers. Tangl, Forster and Zielonko, however, maintained that in cardiac hypertrophy there was enlargement of the individual cells but no increase in number. Tangl furthermore could demonstrate no increase in the number of nuclei and concluded that hypertrophy consisted in increase in size and volume of the individual heart muscle cells. Romberg and Hasenfeld verified these contentions in the rabbit's heart after experimental aortic incompetency. Belints produced with experimental aortic regurgitation in dogs, cats and rabbits, work hypertrophy of the heart that seemed to be closely correlated with the grade of the burden imposed. Stadler found that hypertrophy was not limited to the chamber that bore the brunt of the overload.

Albrecht conceived of physiological as well as morphological properties

of hypertrophied muscle which would insure greater functional capacity. In certain hypertensive chronic nephritics, for instance, he pointed out that the right ventricle, as well as the left, undergoes some hypertrophy, while in other nephritics there is no hypertrophy at all. Albrecht further noted in his own studies and those of others a definite concomitant increase in the inter-



stitial and parenchymatous changes as pathological processes in which hypertrophy may be considered to be only a secondary manifestation. Albrecht felt that toxins and pathologically impaired local myocardial nutrition in chronic nephritics caused interstitial myocardial disease and acted as the stimulus to hypertrophy. A connective tissue increase in the hypertrophied

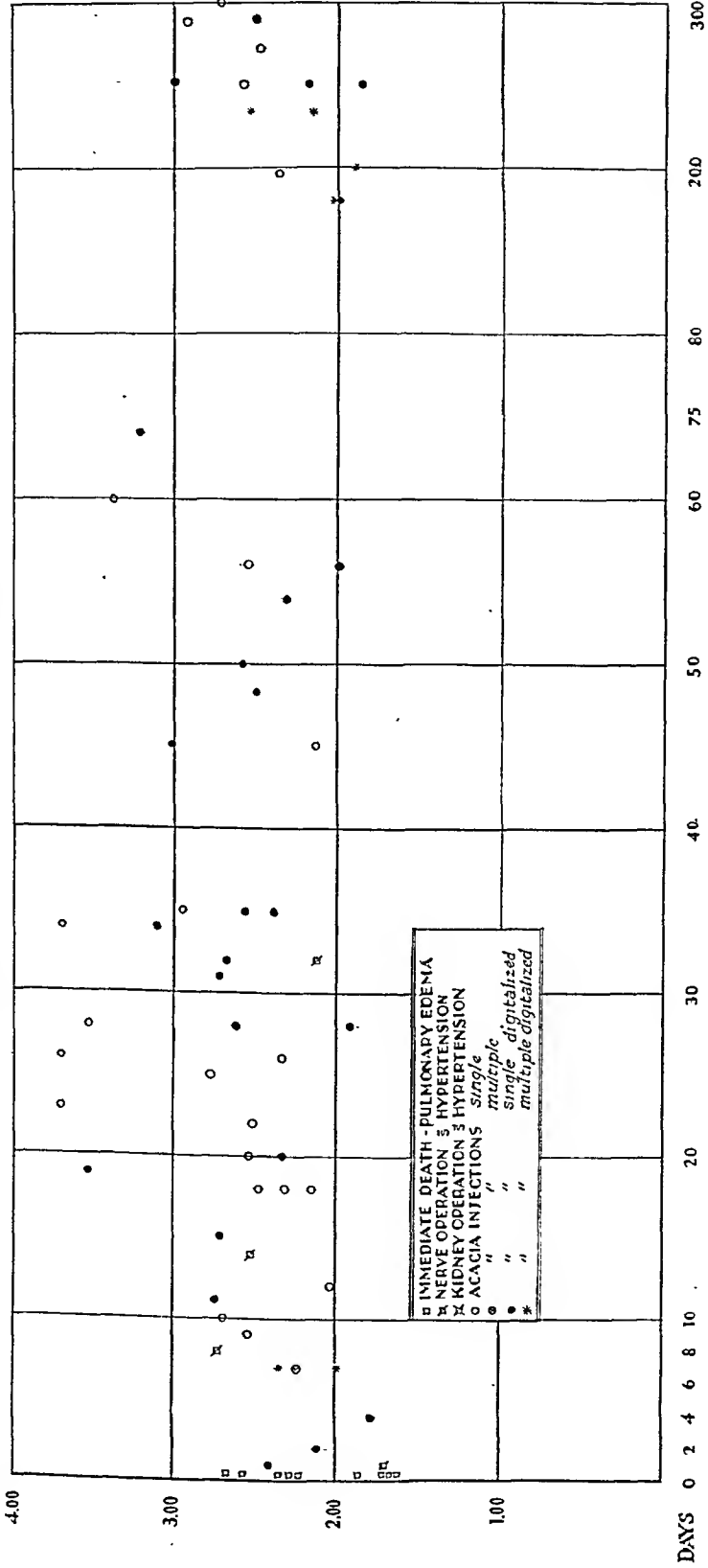
heart has been commented on by others. In this connection it is interesting that in recent studies, Bartels and Smith found cardiac hypertrophy in 26 out of 42 cases with myocardial infarction. Davis and Blumgart reported six greatly hypertrophied hearts out of 31 hearts with advanced coronary sclerosis, and 16 hypertrophied out of 17 with comparable arteriosclerotic disease but with added congestive failure. The congestive failure they therefore thought contributed to the hypertrophy.

Tangl sharply opposed the idea that the interstitial processes had anything to do with hypertrophy, on the basis of the absence of such changes in the early stages of hypertrophy in experimental work. Dehio carefully restudied the whole problem and attributed the myofibrosis to the stasis in the myocardial capillaries incident to the increased diastolic pressure in the dilated ventricle. This he stated is the stimulus to fibroblastic proliferation. There is much argument pro and con in the German literature concerning the significance of these interstitial findings. Albrecht has emphasized the fact that mechanical and chemical toxic stimuli may result in hypertrophy. Horvath revived the law of Fick for skeletal muscle, in which increased initial load and stretching were related to the work, and applied it to the heart. He referred to the stretching of the muscle as the stimulus to hypertrophy.

Starling⁹ propounded the law of the heart which stated the important relation between the initial load represented by the venous pressure, the diastolic volume or the initial length of the ventricular muscle scroll, and the volume output of blood from the heart chambers. He found that co-ordination between the diastolic volume and systolic output of the heart represented by the venous pressure determines the initial length of the ventricular muscle fibers. Abnormal strains increase the initial load and to such may be attributed dilatation or stretching. This is a common precedent to hypertrophy. The significance of the dilatation in both phases of systole and diastole is an increase in the demand on the myocardium and its blood supply. Under such conditions ventricular contraction or systole is accompanied by an incomplete emptying and dilatation in the diastole and by an overfilling of the cavity. The increased pressure must be resisted by the ventricular wall, and a vicious circle is thus created. The dilatation contributes the overstretching stimulus to maximal contraction and hypertrophy. An occasional hypertensive patient's heart which has not been dilated may be the seat of concentric hypertrophy and show relatively little functional incompetency and histologically no fibrosis.

Stewart¹⁰ explained his experimental finding of general hypertrophy involving the right ventricles and the auricles as well as the left ventricles in dogs with aortic regurgitation, on the basis of an intracardiac reflex which coördinated the work of all chambers. Stewart held that parenchymatous damage leads to enlargement of heart muscle cells, and interstitial changes and stretching to myofibrosis. Herrmann^{11a} corroborated Stewart's observations of multichamber involvement and added the observation that in the presence of secondary infectious valvulitis considerably greater degrees of

EXPERIMENTAL STUDIES in CARDIAC HYPERTROPHY
HEART WEIGHT - BODY WEIGHT RATIOS AFTER ACACIA INJECTIONS
POST INJECTION INTERVALS IN DAYS



cardiac hypertrophy resulted than were found in dogs with uninfected aortic regurgitation. In this large series of 70 dogs with experimental aortic regurgitation the age of the animals at the time at which the lesion was produced seemed to be another factor besides infection in determining the grade of hypertrophy. The postoperative interval was likewise of some importance and, although Stewart had reported hypertrophy within 10 days, the earliest evidence in this series was found after 19 days. In studies with Mims Gage ^{11b} the hearts of dogs with experimental arteriovenous aneurysm were shown by heart weight/body weight ratios to be slightly but definitely hypertrophied. In one dog that lived seven years a 100 per cent hypertrophy was produced.

In studies with E. H. Schwab ^{11c} in rabbits with experimental aortic insufficiency the location of the damaged cusp seemed to be significant.

Hartmann ¹² presented data to the effect that cardiac hypertrophy followed the production by roentgen-radiation of nephritis in dogs. Besides teleoroentgenographic and electrocardiographic evidence he found heart weight/body weight ratios up to 0.11 instead of the normal 0.07. There was, however, no definite correlation between the hypertension which was produced in the majority of animals and the degree of hypertrophy. The latter was greater than might be expected from the blood pressure. The hypertrophy seemed to have developed by the time that the hypertension became definite.

Eyster, Meek and Hodges ^{13a} demonstrated by frontal plane teleoroentgenograms an increase in heart volume appearing immediately after aortic regurgitation was experimentally produced in dogs. They found that this enlargement disappeared after a few days and the heart returned to its normal volume or even to subnormal size. Following this there was a gradual hypertrophy which reached a maximum after about 70 to 100 days. A second lesion superimposed on the first caused a second period of transitory dilatation and was followed by a subsequent period of additional hypertrophy. Bazett ¹⁴ questioned the occurrence of the early dilatation as a result of stretching which he was unable to demonstrate. He attributed the apparent enlargement to changes in rate. Holman ^{14b} showed that bleeding an animal followed by subsequent infusion of the same blood gave similar changes in the teleoroentgenograms.

Eyster ^{13b, c} reported macroscopic and microscopic evidence of stretching and injury of the heart muscle during this short period of primary dilatation, and concluded that the stimulus to hypertrophy was the overstretching of the myocardial scrolls to the point of injuring them. Eyster further reported that a constricting rubber band placed around the aorta for three to six days and then removed caused the hearts to hypertrophy progressively thereafter. To test out this hypothesis further Eyster produced temporary cardiac overload, with stretching of the heart muscle beyond its physiologic limits and consequent muscle injury in a series of 11 dogs, by massive transfusions of 75 per cent to 100 per cent of their blood volume. He demonstrated the same changes in the teleoroentgenograms as had followed experimental aortic

regurgitation. On two of these dogs he showed heart size increases of 13.5 per cent lasting five days, decreasing to + 3.5 per cent, rising to + 18 per cent in 122 days, rising to + 22 per cent after the second transfusion, falling to + 10 per cent in seven days, and increasing to + 25.5 per cent on the one hundred sixty-eighth day. So far as we can find out Eyster has not published any heart weights or ratios on the transfused dogs. The experiments should be repeated and the postmortem ratios determined. Eyster stated that a prolonged period of increased work was not necessary to produce hypertrophy, since a single insult, such as a transitory overstretching, would cause hypertrophy.

If the single initial injury hypothesis could be supplemented by the support of actually demonstrated increases in the weights of hearts subjected to temporary dilatation, there would be established a fundamental basis for the explanation of all types of cardiac hypertrophy known to occur in various clinical conditions. In most of these we can assume not only dilatation as a sequel to increased load, but in addition myocardial anoxemia and toxic or inflammatory myocarditis as further factors in initiating hypertrophy. A continuance of the extra burden or a part of it is much more common than a total subsidence of the same. Any pathologic lesion in the myocardium would interfere with the efficiency of the heart action and add to the burden. Hypertrophy in response to inefficient function would then be a manifestation of myocardial weakness.

It is not necessary to comment upon the frequent association of cardiac hypertrophy with valvular lesions and with increased arterial resistance, other than to emphasize the not uncommon absence of any evidences of hypertrophy in the hearts of some patients known to have had hypertension for years antemortem. In contrast to this are the observations of Willius and Smith¹⁷ of hearts with hypertrophy far out of proportion to the valvular lesions in acute rheumatic carditis of known short duration. Similarly marked increase in heart weight is a typical finding in the so-called Fiedler's myocarditis,¹⁸ where valve lesions are absent. Inflammatory edema and infiltration make up a large part of the increase in weight in the acute myocarditis cases and may interfere with efficient function.

Lewis and Drury¹⁵ attributed the cardiac enlargement in arteriovenous fistulae to *impaired coronary filling*, though this does not adequately explain the preponderant enlargement of the right side of the heart, nor does it, as Porter and Baker¹⁶ point out, seem reasonable as the sole explanation of a phenomenon that will largely disappear within a few weeks after closure of the fistula. The cause in our opinion, is a combination of dilatation and decreased coronary blood flow.

Smith and Bartel's¹⁹ group of cases with hearts from 9 per cent to 108 per cent larger than normal (averaging 44 per cent) with no factor predisposing to this other than *occlusion* of one or more of the *coronary* vessels is difficult to explain. The possibility of a previous hypertensive state has not been absolutely ruled out. The findings have been denied by both clini-

cal and experimental investigators. In addition, occasional cases have been seen of hypertrophy in hearts whose left coronary supply had an anomalous origin from the pulmonary artery. Davis and Blumgart²⁰ have recently advanced strongly suggestive evidence that coronary arteriosclerosis may be the sole etiologic agent leading to myocardial hypertrophy, though unfortunately they make no note concerning the renal arterioles in their cases, and hence may have included cases of subsided essential hypertension.

Anemia, though this is uncommon clinically, may appear to be the sole factor that is associated with an hypertrophied heart, and this set of circumstances has been duplicated experimentally. Again, while the evidence is not conclusive that *lowered oxygen tensions* may lead to cardiac hypertrophy in humans, in experimental animals marked reduction of the barometric pressure, or decrease in the oxygen content of the environmental atmosphere will lead to indisputable increases in the heart weights. In short, sharp increase in the ventricular load, inflammatory changes in the myocardium, or myocardial anoxemia, all of which lead to cardiac dilatation, are conceivable factors in all types of cardiac hypertrophy.

THE PRESENT STUDIES

The Rabbit Series. Our experiments were designed to test out the theory of initial injury as the stimulus to progressive cardiac hypertrophy. As the initial load that would produce cardiac dilatation and strain, we used 6 per cent and 12 per cent buffered acacia solution, introduced rapidly intravenously in a volume equal to the blood volume, or $\frac{1}{14}$ of the animal's weight. Most of the series of rabbits averaged three months in age and weighed about three pounds each. They were given the acacia solution through the ear veins under pressure, over a period of five to 15 minutes. More than 100 rabbits were used, of which about 10 per cent died immediately as a result of acute pulmonary edema. This was considered conclusive evidence that there was a maximal strain put on the heart by this procedure.

After the injection of the acacia solution in the series the hemoglobin was routinely found to be about 50 per cent of what it had been previously, indicating about what dilution of the blood had been made. In general, the hemoglobin level was back to normal in four to seven days after the first injections. In a small series of animals the acacia injections were repeated at weekly intervals for two or three weeks, maintaining the hemoglobin at about 50 per cent to 75 per cent of normal. In these the hemoglobin took somewhat longer to return to normal.

After the injections the animals were divided into two groups. In the first group nothing further was done (the animals were fed and kept in small individual cages), whereas the other group received regularly, twice a week, 0.25 cat units of Digalen* or Digifolin.† The rabbits were sacrificed at

* Supplied by Hoffmann La Roche Co., Nutley, N. J.

† Supplied by Ciba Co., Summit, N. J.

varying periods of time from a few days to 300 days. The hearts were removed and carefully weighed, the body weight was taken, and HW/BW ratios were estimated. As a normal for this series we used the HW/BW ratio for rabbits of the same age from the same source, that had had carotid sinus operations without the production of hypertrophy (HW/BW 2.16), and rabbits that had had unilateral nephrectomy and the cutting down of the circulation of the other kidney without resulting hypertension (HW/BW 2.25).

The mean for the HW/BW ratios of the rabbits that had been given a single injection of acacia alone and not treated otherwise was higher (2.68) than that for any other group, but the increase was not statistically significant. There was, however, no further increase in HW/BW ratio whatsoever nor any significant difference between the animals sacrificed after 62 days (HW/BW 2.83), 240 days (HW/BW 2.58), and those sacrificed after about 300 days (HW/BW 2.71).

The rabbits that had received a single acacia injection and were subsequently digitalized showed a slightly lower mean HW/BW ratio (2.57) but again the difference was not statistically significant. Likewise the animals that were digitalized before the acacia solution was given had a still lower mean HW/BW ratio (2.37) which is also not statistically significant. The few animals that received 6 per cent acacia had slightly smaller hearts than those that were infused with 12 per cent acacia, but this was not established statistically. Multiple acacia injections with the persistent anemia produced for three weeks did not seem to act as a stimulus to hypertrophy. The multiply injected acacia animals that were digitalized had the lowest HW/BW ratio mean of the group (2.08), but there were so few of them that they were not statistically significant. The HW/BW ratios in these series were higher than those that we have gotten as our previous normal HW/BW ratio (1.98) but not higher than the normals of other investigators, nor were they higher than the normals for the present series.

The White Rat Series. White rats of the Wistar strain and of the Yale strain were injected with 12 per cent buffered acacia solution in a volume equal to $\frac{1}{14}$ the body weight, just as the rabbits had been injected. The calculated amount of solution was introduced into the rats through the femoral vein, within a period of about five minutes. Many developed pulmonary edema, but only 5 per cent died from it. Twenty of the rats were males of the Wistar strain weighing 200 to 300 gm. and had previously been operated upon and had the blood supply to the left kidney reduced by a ligature (using a wire similar to Collins', 0.4 mm. in diameter) over the artery. None of these white rats showed any hypertension subsequent to the operation, in fact the blood pressures ranged from 60 to 100 mm. of mercury. The other 20 were fresh Yale strain males weighing 175 to 225 gm. each.

Only 20 days were allowed for the hypertrophy to develop in these two

series of rats, but this seemed to be sufficient since in other studies, particularly Rytand's,²¹ hypertrophy was reported to have developed after a comparable length of time following renal artery compression. The HW/BW ratio mean of the operated Wistar rats that had been injected with acacia was slightly higher (3.22) than that in the rats of the Yale strain series in which acacia alone was given (3.04). Thus the differences from normal were not significant. Both means were lower than the normal HW/BW ratio calculated from Addis' formula, which was 3.40 for rats weighing between 150 and 250 gm., while the normals in our own series that had died acutely at operation or during the experiment gave a normal HW/BW ratio of 3.37.

COMMENTS

These experimental data from both the rabbit series and the rat series fail to corroborate, with statistically significant differences, the Horvath-Eyster hypothesis. The stretching of the heart with an overload of acacia solution to the point of producing pulmonary edema is perhaps not strain enough to exhibit initial injury of the necessary grade.

TABLE I
Data on Attempts to Produce Cardiac Hypertrophy in Rabbits

Experiment	No.	HW/BW Ratio Mean \pm PE _{Mean}	Standard Deviation
1. Nerve operations—No hyp.....	5	2.16 \pm 0.12	0.42
2. Kidney operations—No hyp.....	25	2.25 \pm 0.06	0.46
3. Acacia-pulmonary edema.....	13	2.25 \pm 0.08	0.42
4. Acacia injection alone.....	27	2.68 \pm 0.07	0.53
5. Acacia and digitalis.....	22	2.57 \pm 0.06	0.44
6. Predigitalized acacia.....	5	2.37 \pm 0.09	0.30
7. Multiple acacia.....	4	2.44 \pm 0.11	0.33
8. Multiple acacia and digitalis.....	4	2.08 \pm 0.08	0.24

TABLE II
Heart Weight/Body Weight Ratios on White Rats 20 Days after Injection of Acacia

	HW/BW Ratio Mean \pm PE _{Mean}	Standard Deviation
1. Normal (Addis) *.....	3.40 \pm 0.06	0.43
15. Normal (ours).....	3.37 \pm 0.09	0.52
20. Previously operated—Acacia later.....	3.22 \pm 0.08	0.54
20. Acacia only (Yale).....	3.04 \pm 0.05	0.36

* Calculation from Addis formula for rats, 150–250 gm.

The acacia solution should have been as effective as Eyster's 75 per cent to 100 per cent increases in blood volume transfusion. Eyster's conclusions, therefore, cannot be substantiated.

We were further disappointed in that the digitalized acacia rabbit series did not show statistically significant differences from the non-digitalized series. The mean HW/BW ratios were lower but not significantly so. We may thus question the validity of Cloetta's conclusions.

On the basis of our data we feel that the injury that results from temporary dilatation alone is not sufficient to produce cardiac hypertrophy.

BIBLIOGRAPHY

1. HARRISON, T. R., ASHMAN, R., and LARSON, R. M.: Congestive heart failure: relation between thickness of cardiac muscle fiber and optimum rate of heart, *Arch. Int. Med.*, 1932, xlix, 151.
2. WEARN, J. T., ROBERTS, J. T., and BADAL, J. J.: Capillary-muscle ratio in normal and hypertrophied human hearts, *Proc. Soc. Exper. Biol. and Med.*, 1938, xxxviii, 322.
3. CHRISTIAN, H. A.: The use of digitalis other than in the treatment of cardiac decompensation, *Jr. Am. Med. Assoc.*, 1933, c, 789.
4. CLOETTA, M.: The effect of digitalis upon the normal and pathologic heart, *Arch. Exper. Path. and Pharm.*, 1908, lix, 209.
5. MATAS, R., and HENINGER, B. R.: Reversible cardiac enlargement in a case of congenital cavernous hemangioma, *Am. Heart Jr.*, 1939, xvii, 131.
6. TUNG, C. L., HSIEH, C. K., BIEN, C. W., and DIEUAIDE, F. R.: The hearts of ricksha-pullers, *Am. Heart Jr.*, 1934, x, 79.
7. ROBB, G. P., and STEINBERG, I.: Visualization of the chambers of the heart, *Am. Jr. Roentgenol. and Therap.*, 1939, xli, 1.
8. MÖNCKEBERG, J. G.: Myokard und spezifisches Muskelsystem bei Störungen des Klappenmechanismus und bei sonstigen zur Hypertrophie führenden Erkrankungen, *Handbuch der speziellen pathologischen Anatomie und Histologie*, Band II, Herz und Gefäße. 1924, ii, 349.
9. STARLING, E. H., and VISSCHER, M. B.: The regulation of the energy output of the heart, *Jr. Physiol.*, 1927, lxii, 16.
10. STEWART, H. A.: The mode of action of adrenalin in the production of cardiac hypertrophy, *Jr. Path. and Bact.*, 1912-13, xvii, 64.
- 11a. HERRMANN, G. R.: Experimental heart disease. II. With a consideration of some factors concerned in cardiac hypertrophy, *Am. Heart Jr.*, 1926, i, 485.
- 11b. GAGE, I. M., and HERRMANN, G. R.: Cardiac hypertrophy in A-V aneurysm, *Proc. Soc. Exper. Biol. and Med.*, 1928, xxv, 765.
- 11c. SCHWAB, E. H., and HERRMANN, G. R.: Experimental ablation of posterior as contrasted to anterior aortic cusp on cardiac hypertrophy in rabbits, *Proc. Soc. Exper. Biol. and Med.*, 1935, xxxiii, 410.
12. HARTMANN, F. W., BOLLINGER, A., and DONL, H. P.: Cardiovascular response in experimental nephritis, *Jr. Am. Med. Assoc.*, 1927, lxxxix, 1936.
- 13a. EYSTER, J. A. E., MEEK, W. J., and HODGES, F. J.: Cardiac changes subsequent to experimental aortic lesions, *Arch. Int. Med.*, 1927, xxxix, 536.
- 13b. EYSTER, J. A. E.: Cardiac dilatation and hypertrophy, *Trans. Assoc. Am. Phys.*, 1927, xlii, 15.
- 13c. EYSTER, J. A. E.: Experimental and clinical studies in cardiac hypertrophy, *Jr. Am. Med. Assoc.*, 1928, xci, 1881.
- 14a. BAZETT, H. C.: Further observations on experimental aortic regurgitation, *Am. Jr. Physiol.*, 1925, lxxii, 201.
- 14b. HOLMAN, E.: Significance of temporary elevation of blood pressure, following splenectomy with particular reference to rôle of spleen as a regulator of circulation, *Surgery*, 1937, i, 688.

15. LEWIS, T., and DRURY, A.: Observations relative to arteriovenous aneurysm, *Heart*, 1923, x, 301.
16. PORTER, W. B., and BAKER, J. B.: The significance of cardiac enlargement caused by arteriovenous fistula, *ANN. INT. MED.*, 1937, xi, 370.
17. WILLIUS, F. A., and SMITH, H. L.: Factors concerned in cardiac hypertrophy, *Am. Heart Jr.*, 1934-35, x, 190.
18. SCOTT, R. W., and SAPHIR, O.: Acute isolated myocarditis, *Am. Heart Jr.*, 1929, v, 129.
19. BARTELS, E. C., and SMITH, H. L.: Gross cardiac hypertrophy in myocardial infarction, *Am. Jr. Med. Sci.*, 1932, clxxxiv, 452.
20. DAVIS, D., and BLUMGART, H. L.: Cardiac hypertrophy: its relation to coronary arteriosclerosis and congestive heart failure, *ANN. INT. MED.*, 1937, xi, 1024.
21. RYTAND, D. A.: Renal factor in arterial hypertension with coarctation of the aorta, *Jr Clin. Invest.*, 1938, xvii, 391.

A METHOD OF TESTING CARDIAC FUNCTION *

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THE PROBLEM

For a period of 10 years we have interested ourselves in the effect of athletic exercise upon the heart. These observations, on more than 400 athletes during their university residence, were presented to the American Student Health Association at its 1937 meeting in Chicago and were published in the Proceedings of the organization.

The result of these observations indicated definitely that the response of the heart to exercise depended not upon the exercise but upon the integrity of the heart's mechanism, and that hearts with slight departures from perfection in their mechanism were much more common among athletes than had been generally assumed. If this defect impaired the ability of the heart normally to carry out its function, the heart compensated for this by enlargement, whereas the undamaged heart of an athlete undergoing the same amount of exertion in the same sports would be normal in size.

During this period of observation, it was found that the percentage of enlarged hearts varied from year to year, the extremes being 6 per cent and 17 per cent, and the average being about 10 per cent. Each year it was found that the athletes whose cardiac measurements were above normal presented evidence of cardiac damage.

The procedure of estimating cardiac size is not a simple one. There is not a uniformity of opinion in regard to how accurately this can be done. We have sought for a method by which heart size can be accurately measured. The heart being a three-dimensional organ, its size may be expressed by volume or by weight.

Bardeen has checked the relation between heart volume, transverse diameter, and area, by anatomical measurements in the cadaver, and he found that their interrelation was sufficiently constant to justify the use of transverse diameter and area as an index of heart volume.

For practical purposes radiological measurements of the heart are limited to the transverse diameter and area of the frontal silhouette. Area involves, besides the experimental error in obtaining the heart outline, a further error in measuring it, and for this reason we prefer the transverse diameter as the index of the heart size. The volume of the heart varies directly with the cube of the transverse diameter so that quite small changes in transverse diameter correspond to considerable changes in volume. The relation of transverse diameter to volume is not a constant one for it varies with the position of the heart in the chest. This variation in the lie of the heart is

* Received for publication August 26, 1938.

From the Student Health Service of the University of Missouri.



FIG. 1. Stethoscope applied to chest at beginning of test.



FIG. 2. Test carried out at the rate of 35 squats per minute.

roughly neutralized if the transverse diameter is correlated with both body height and weight.

We have felt that the transverse diameter of the heart can be fairly accurately measured by roentgen-ray and that it is the most satisfactory and practical guide for estimating the size of the heart.

The left auricle may enlarge without affecting the transverse diameter, but we will describe later a technic for estimating its size. An increase in size of any of the three remaining chambers will result in an increase in the measurement of the transverse diameter.

M. R. Student. Track (2 mile run); aged 21; ht. 68½ in.; wt. 161 lbs.

Transverse diameter. 14.2 cm. Esophagram—no distortion. E. K. G. normal. No murmurs.

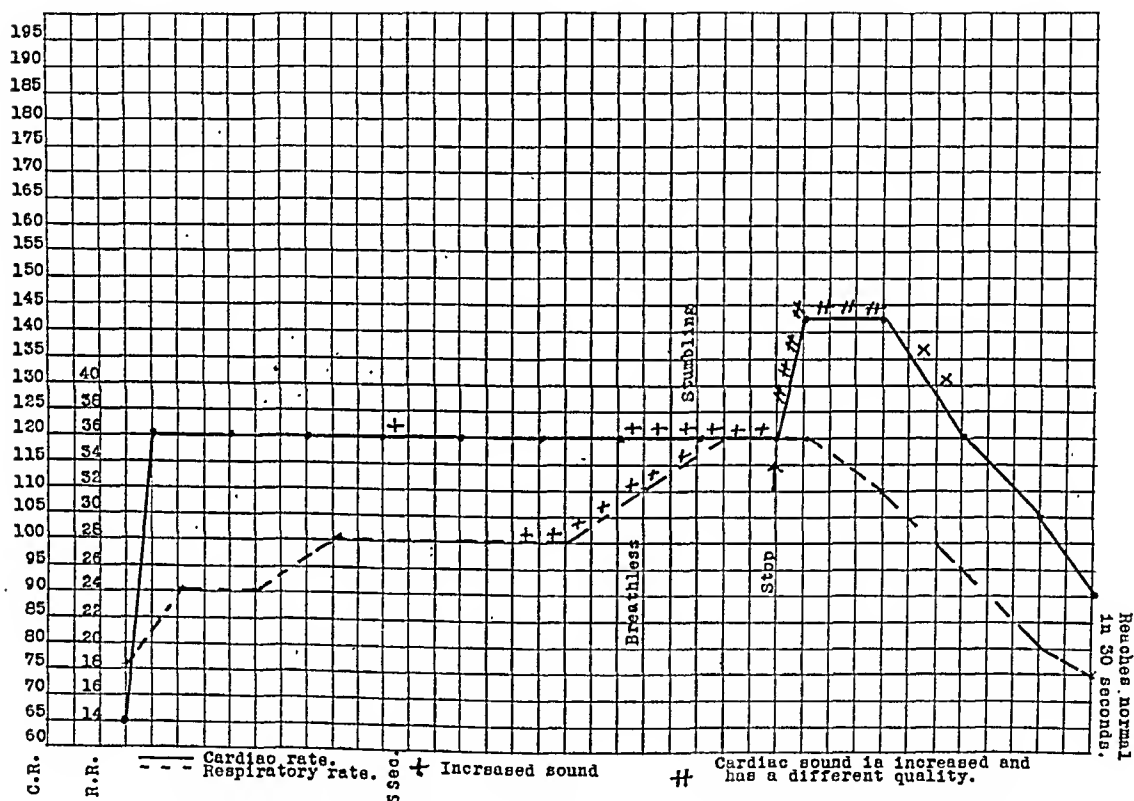


CHART 1. An excellent response to the test by a normal, well trained heart.

A definite decision as to whether or not a heart is enlarged can be made only if the transverse diameter is compared with some standard which will state what the diameter of the heart of an individual should be, if that individual's heart were normal.

In 1919, Danzer suggested the use of a ratio between the cardiac and thoracic transverse measurements as a standard. According to this standard, a heart is normal in size when its transverse diameter approximates one-half the internal diameter of the thorax, and is enlarged when the transverse diameter exceeds 50 per cent of the internal diameter of the thorax. In our

Hodges and Eyster have employed their formula (the transverse diameter of the heart $= + 0.1094 \times \text{age} + 0.8179 \times \text{weight} - 0.1941 \times \text{height}$) in drawing up a table from which one can predict the normal transverse diameter of the heart of the individual with an error of less than 5 mm. This table was used in predicting the normal transverse diameter of the hearts of the athletes that we examined.

Having satisfied ourselves that we could determine when a heart was enlarged, and finding this enlargement was limited to a small percentage of

Ernest L. B. Student; aged 23; ht. 70 in.; wt. 160 lbs.
Transverse diameter. 11.5 cm. Esophagram—no distortion. Double mitral murmur and thrill. E. K. G. normal.
Well compensated mitral disease.

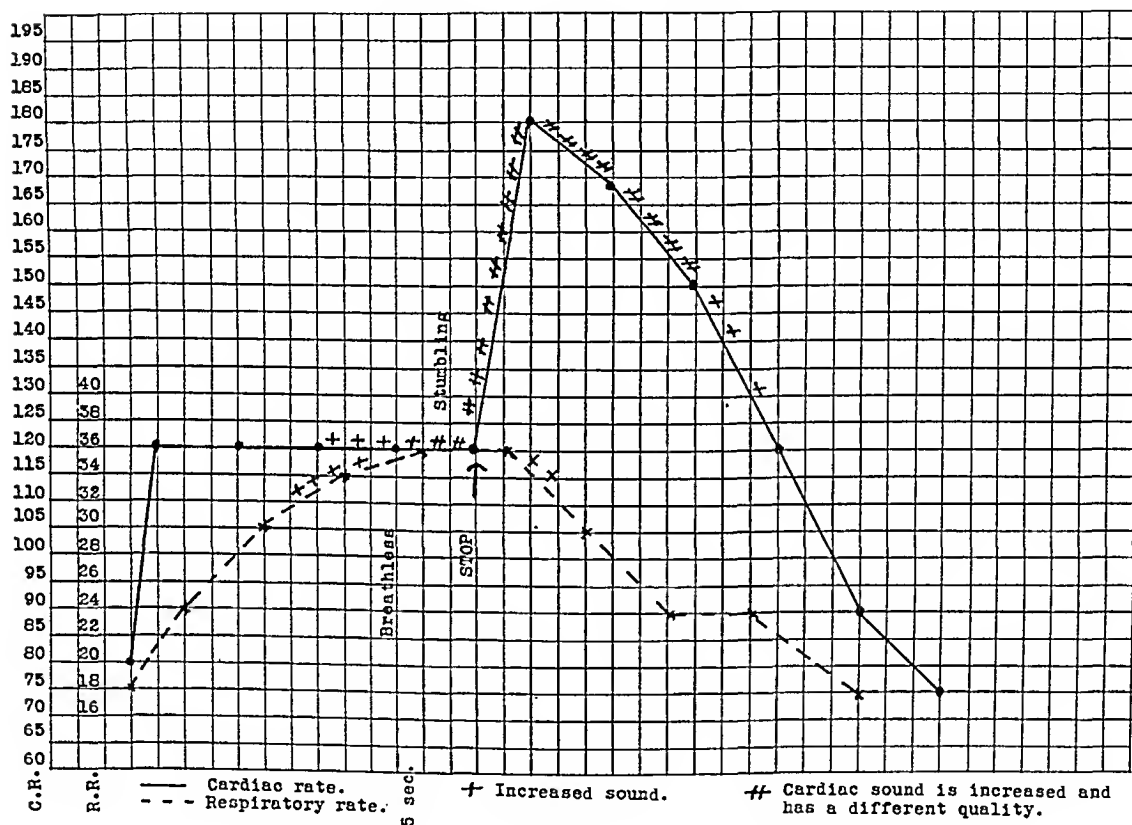


CHART 3. A good test in spite of physical signs of mitral disease of the heart.

athletes not engaged in any special sport, we could expect to find an explanation of the hypertrophy in the heart itself.

To our surprise there did not seem to be any relationship between cardiac damage, the size of the heart, and the individual's athletic prowess.

It was noted that cardiac hypertrophy due to the strain of exercise upon slightly damaged hearts was established during the period of athletic exertion in high school, and that an additional increase in size was rarely noted when the athletes were followed through their four years of university competitive sports.

To determine that a heart is normal requires a very complete cardiac examination and we have found the following data necessary:

- 1. The type of athletic sport that the individual is engaged in.
- 2. The height, weight, and age.
- 3. The transverse diameter of the thorax.
- 4. The transverse diameter of the heart shadow as shown by the tele-roentgenogram or orthodiagram.
- 5. The predicted normal transverse diameter as given for the individual's height, weight, and age.

Geo. W. H. Student; aged 24; ht. 73½ in.; wt. 187 lbs.
Transverse diameter. 16.5 cm. Esophagram—distorted. E. K. G. Left preponderance and impaired conduction.
Rheumatic fever 1936 and 1937. Mitral disease—poorly compensated.

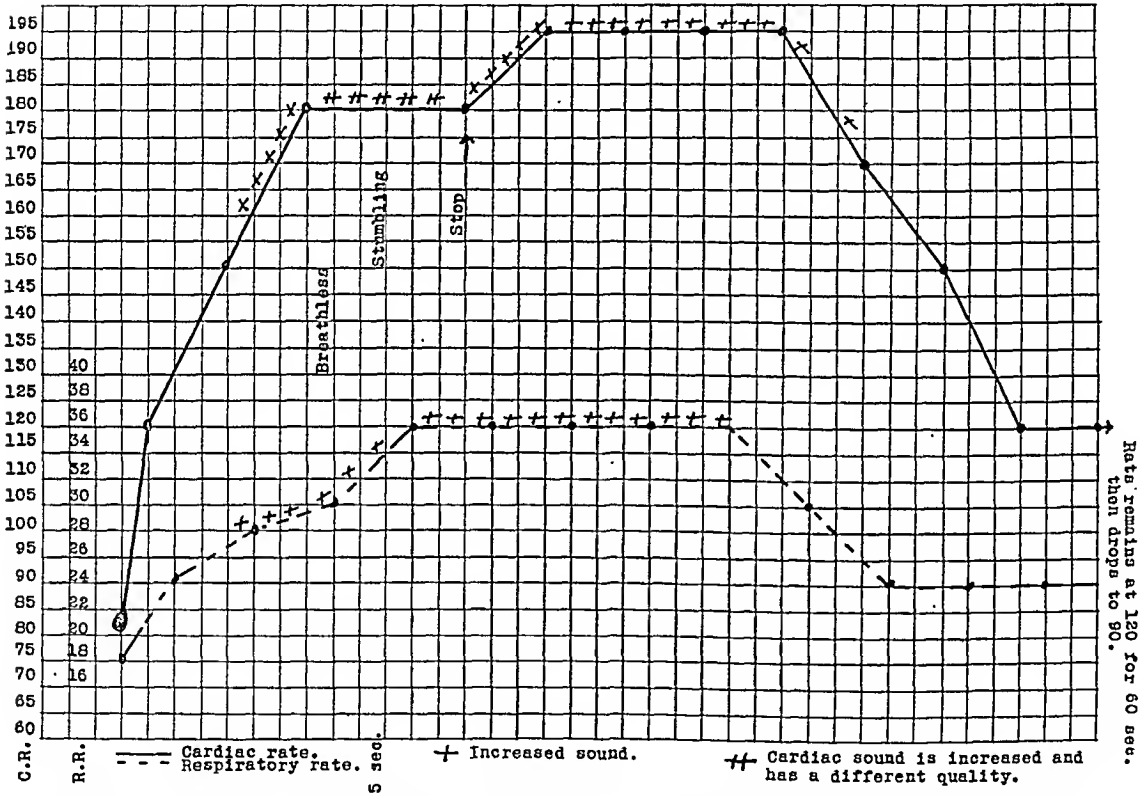


CHART 4. A lack of control of the working rate of the heart in a badly damaged heart due to valvular disease. Note plateau of rest.

6. A film taken of the position of the esophagus in the right oblique lateral position, to determine the size of the posterior chamber of the heart (left auricle) as shown by its indentation of the esophagus, and an antero-posterior film to show lateral displacement of the esophagus by the same chamber, the films being taken immediately after the swallowing of a mouthful of barium paste. We found that any enlargement of the left auricle first compresses the esophagus, and then displaces it laterally to the right.

Any enlargement of the left ventricle of sufficient size to rotate the heart displaces the esophagus laterally to the left.

7. The blood pressure should be taken.*

8. Palpable thrills have to be noted.

9. The presence of a murmur has to be sought for in the upright and in the prone positions after rest and during exercise, and its character and position in the cardiac cycle noted.

Robert P. Student; aged 20; ht. 72½ in.; wt. 138 lbs.

Transverse diameter. 10.5 cm. No murmurs. Esophagram—no distortion. E. K. G. partial heart block. Auricular fibrillation.

No cardiac history.

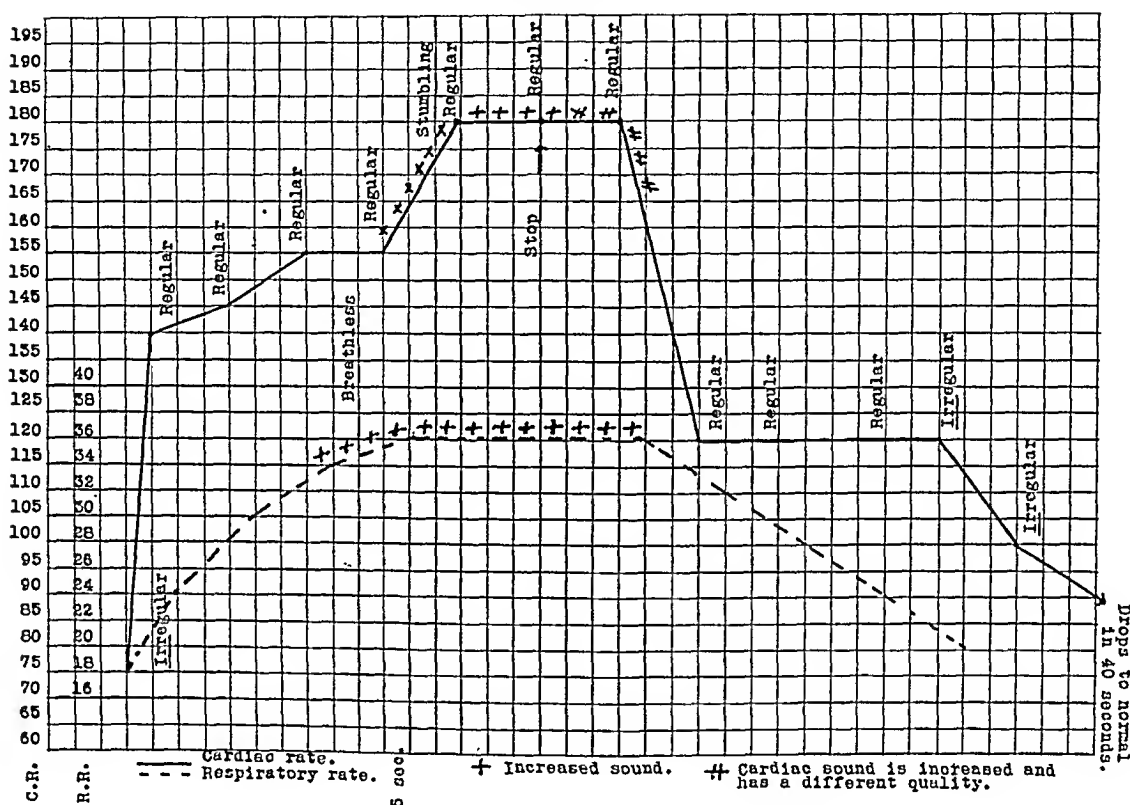


CHART 5. A lack of ability to control the resting rate of the heart due to interference with conductivity within the heart. Note plateau of rest. Also note that the heart rate becomes regular while under stress.

10. Special attention has to be given to the cardiac first sound at the apex and the second aortic sound over the aortic area.

11. An electrocardiogram should be studied.

12. Each patient should be put through a cardiac fatigue test which is usually spoken of as a cardiac function test. The purpose of the usual cardiac function test is to produce cardiac fatigue and estimate how quickly the heart recovers from it.

* All the athletes tabulated in these data had a blood pressure within normal range.

As it is not practical to demand a complete cardiac examination of all high school athletes, we have developed a cardiac function test that corresponds in its results with the rest of the cardiac examination and that will help to identify the individual whose heart is embarrassed, for it is evident that cardiac examinations carried out in high school and even in the university overlook a small per cent of hearts that are damaged.

We are led to believe that strenuous physical exercise produces no change in the normal heart and that the response of the slightly damaged heart to

Clyde E. B. Student; aged 22; ht. 66½ in.; wt. 140 lbs. Nonathletic.
Transverse diameter. 11 cm. Esophagram—no distortion. E. K. G. Hypersensitivity of myocardium.
Vagohypotonia—fainting, sweating, flushing, etc.

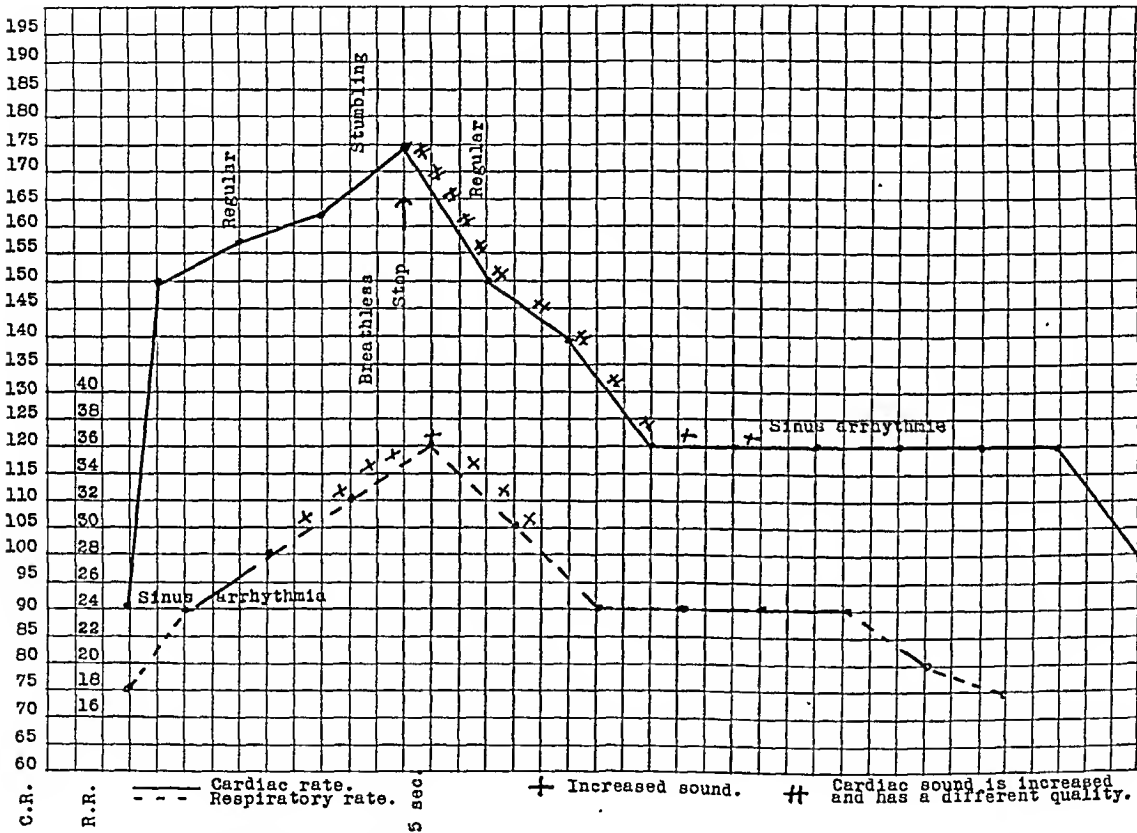


CHART 6. Lack of control of rate, due to vagohypotonia. Note that evidence of Starling's cycle does not appear until rest. Note plateau of rest. Also note that rate becomes regular under stress.

this same amount of exertion is hypertrophy. As this is an abnormal condition that is not desirable, great care should be exercised early in life to guard these individuals against the hazard of too great physical exertion.

THE CARDIAC FUNCTION TEST

A cardiac function test is simply a test to determine how an individual's heart responds to work, and should be carried to the point of fatigue in each instance.

In dealing with the age group of high school and university students where there are some individuals trained to long continued athletic exercise, and other individuals having no bodily training at all, a standard test is necessarily futile, so it became necessary to evolve a test that could be carried out to the point of fatigue in each individual tested. This was done by bandaging a Bowles' stethoscope, with a 5 cm. bowl, and six feet of rubber tubing over the precordia. Then the individual was exercised in the squatting, or sitting-up exercise which quickly fatigues even the trained

Geo. R. Track (running); aged 23; ht. 74 in.; wt. 177 lbs.
Transverse diameter. 14.3 cm. Esophagram—no distortion. E. K. G. Normal.
No murmurs.

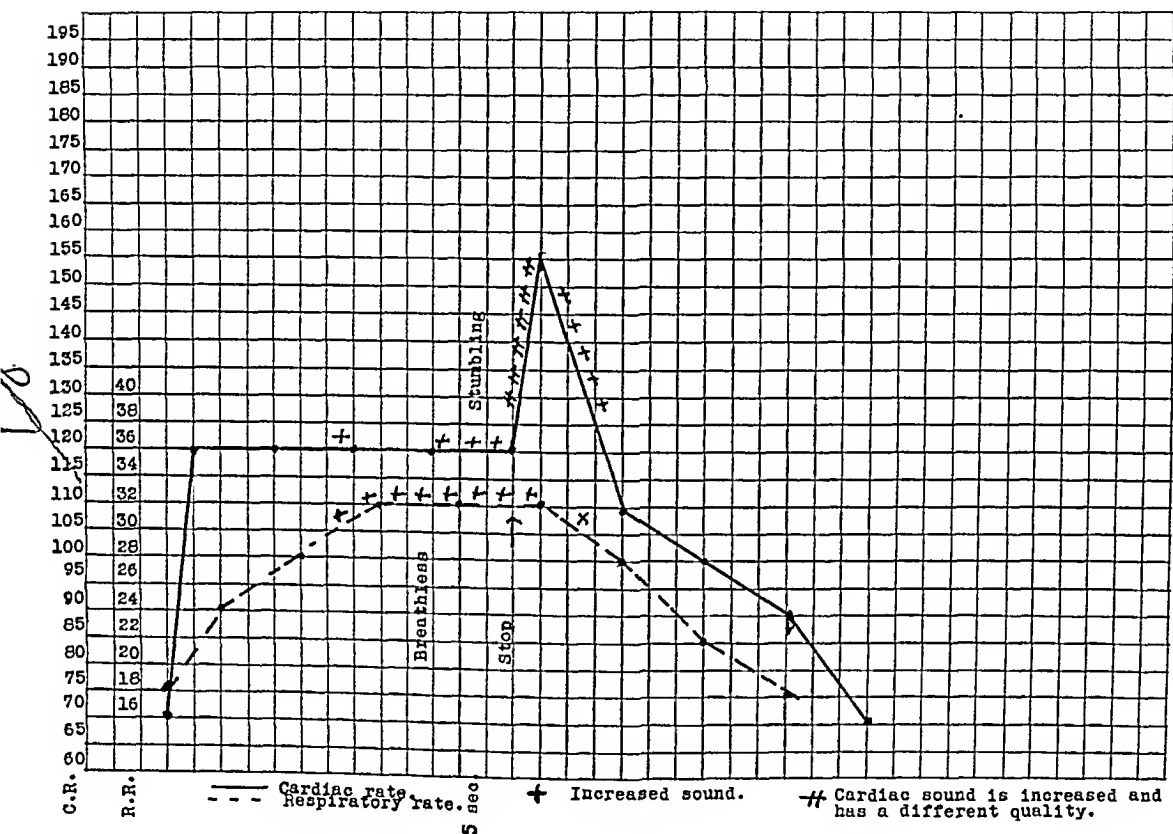


CHART 7. A good test in a normal, well trained heart.

athlete. This was carried to the point of exhaustion in every instance—exhaustion being indicated by a flushed face, breathlessness, and stumbling.

The pulse was taken during rest before exercise, and for every 10 seconds during exercise, with five-second intervals to record the rate—this making a notation of the cardiac rate at every 15 seconds. These records were reduced to graphic charts, and after the test had been used in several hundred instances a number of interesting phenomena were observable.

The heart is a positive pressure pump which most precisely adapts itself

to the constantly changing requirements of the body. This adaptation consists, as in any other pump, in changing the strength of each contraction and in changing the frequency of the contractions, responding thus to the demands of the systemic circulation by both the strength of the heart beat and by the rate of the heart's contractions.

The regulation of the heart rate is a function of the nervous system, whereas the adaptation of the heart for the purpose of a greater output is intrinsic in the heart itself—the heart being able to increase its normal output many times, by increasing the tonicity of its muscle and providing for

Geo. R. After $\frac{1}{100}$ gr. atropine sulphate—hypo.

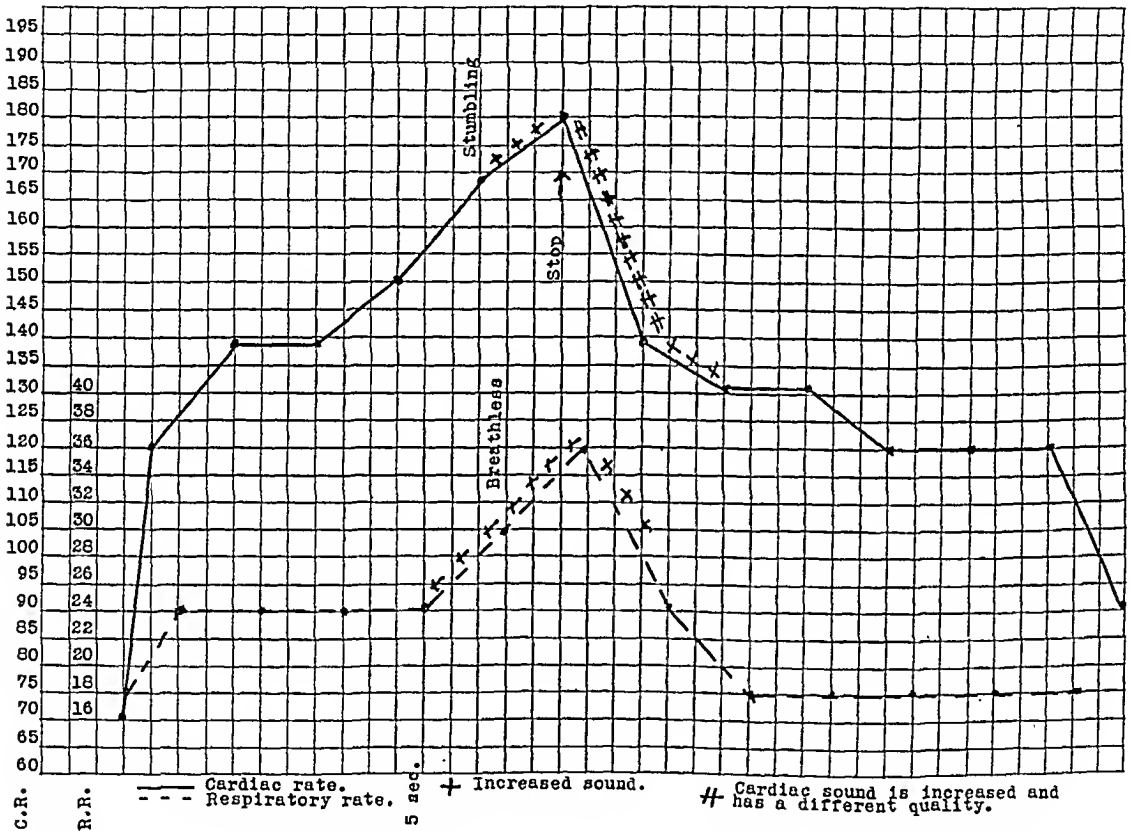


CHART 8. No. 7 after the administration of atropine. Note how closely it resembles No. 6 with vagohypotonia.

dilatation of the chambers by the lengthening of its muscle fiber. These changes take place from beat to beat in answer to the requirements brought about by changes in the systemic circulation.

Out of the great mass of investigative material that has been published in connection with the heart rate and cardiac output, we wish to call attention to the three following factors:

First, it was suggested by Marey, and has been called Marey's Law, that the heart rate has an inverse relation to the blood pressure, that is, the higher the pressure the lower the rate.

Heymans and Ludwig have shown that the slowing of the pulse is due to the effect of an increase in blood pressure on the nerve ends in the aorta. Later, Hering added the effect of this same pressure in the carotid sinus, both acting reflexly on the vagus to slow the rate of the heart.

Second, Starling and others have shown that the essential factor governing the output of the heart is the inflow; that within physiological limits the force of the heart's contraction depends upon the extent to which the heart muscle has been stretched by incoming blood; that by increased tonicity

C. A. L. Inactive; aged 27; ht. 72½ in.; wt. 204 lbs.
Transverse diameter. 12 cm. Esophagram—no distortion. E. K. G. Normal.
No murmurs.

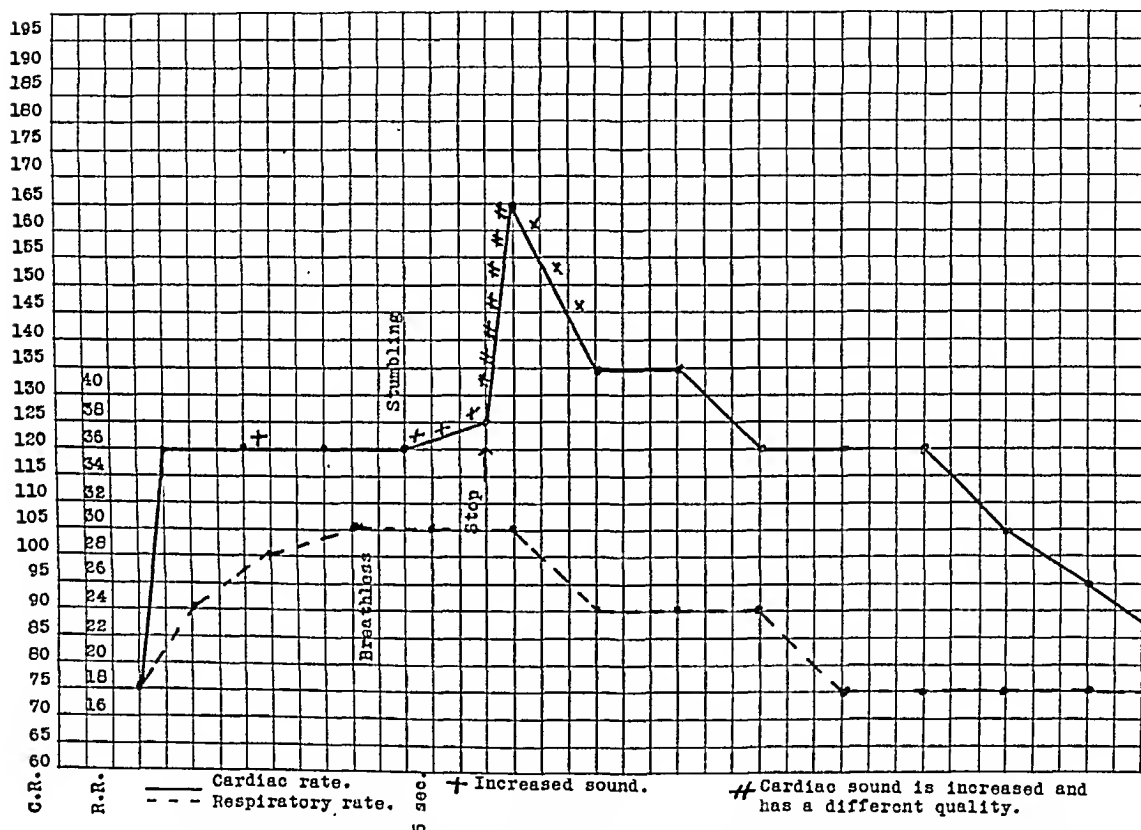


CHART 9. A poor test in a fat, inactive individual. Working plateau is not fully sustained. There is a resting plateau of 30 seconds.

(strengthening of beat), and dilatation (lengthening of cardiac muscle fiber), the heart increases its output at the demand of an increased inflow.

Third, the rate of the heart responds to venous pressure. As shown by Bainbridge, the heart reacts to an increased venous return, that is, dilatation of the great veins entering the right auricle and the right auricle itself, by acceleration of the rate of the heart. This acceleration is evidently reflex in character—the reflex path running to the vagi and also to the accelerator nerves, the acceleration being the result of a reciprocal action between the two sets of nerves, but being due chiefly to diminution of the vagus tone.

Nowhere, however, is there mention of any controlling factor of rate above the resting level at 75 beats per minute. Bowen, in his work on bicycle riders, briefly mentions that the rate tends to reach a plateau during sustained exertion. MacWilliam's work on the effect of chloroform on the cardiac rate in cats mentions that after the initial excitement the rate tends to stabilize at a high level. No deductions were drawn from either of these observations.

In view of these brief facts, taken from many, pertaining to the heart, let us look at the results of our fatigue test in a normal patient. His rate, at

C. A. L. After $\frac{1}{100}$ gr. atropine sulphate—hypo.

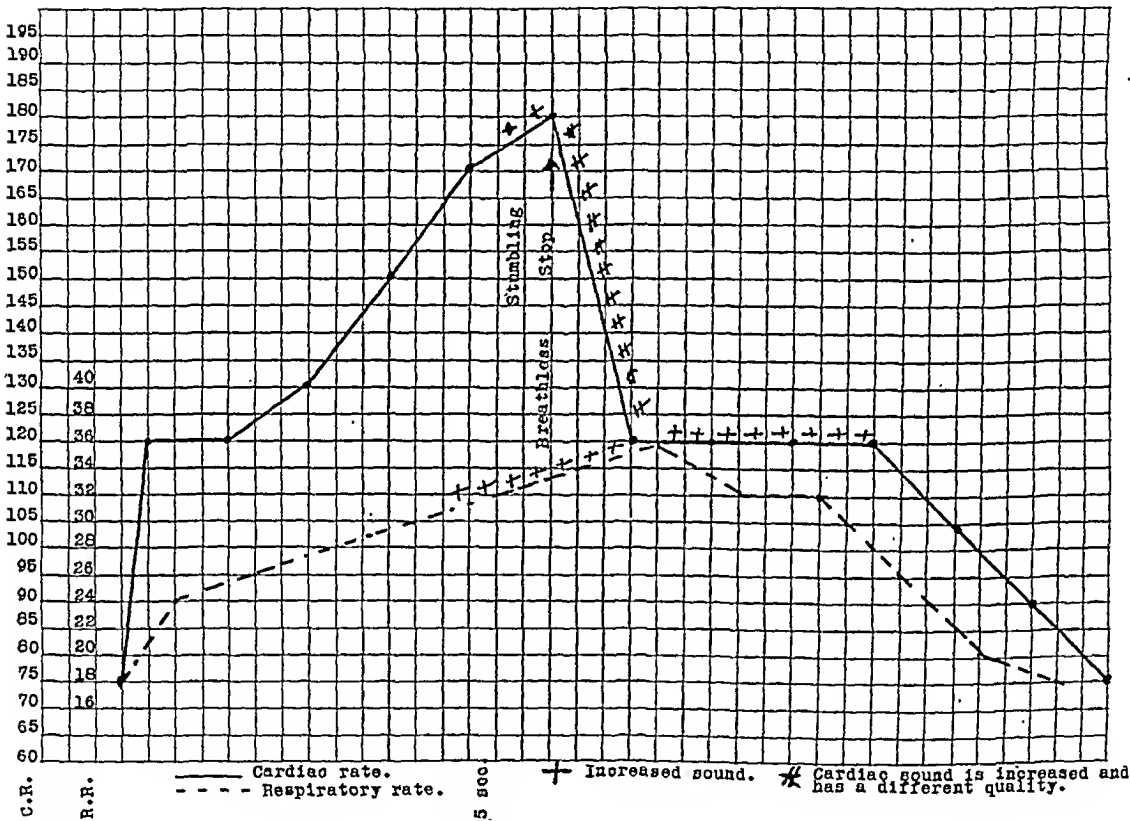


CHART 10. No. 9 after the administration of atropine. The graph more closely resembles that of vagohypotonia.

rest, is in the near neighborhood of 75 beats per minute, which is the result of a nice balance between the accelerator and depressor nerves of the heart.

Immediately on exercise, usually starting within one cardiac cycle, there is a rapid rise in rate due to the institution of the mechanism of the Bainbridge reflex. In well-trained athletes with normal hearts there may be a pause of two or three cardiac cycles before the increase in rate is inaugurated. This acceleration is due chiefly to the diminution of the vagus tone, and slightly to the increased accelerator tone—this being brought about reflexly from the dilatation of the mouths of the greater veins of the right auricle

with venous blood. Instead of this acceleration continuing indefinitely to the point of exhaustion of the heart, we find by our test that this acceleration continues until, within five seconds, it reaches 120 beats per minute, or in the very close neighborhood of 120 beats per minute, and remains at this rate until the individual becomes exhausted. Evidently the rise in rate is stopped by the working of the modern conception of Marey's Law (the increase in aortic and carotid pressure reactivating the depressed vagus function), bringing about a new equilibrium that forms a normal working pulse rate of 120

Arthur D. Inactive for 2 years; aged 22; ht. 76 in.; wt. 165 lbs.
Transverse diameter. 11.3 cm. Esophagram—no distortion. E. K. G. Normal.

No cardiac murmurs.

Vagohypotonia—fainting, sweating, flushing, etc.

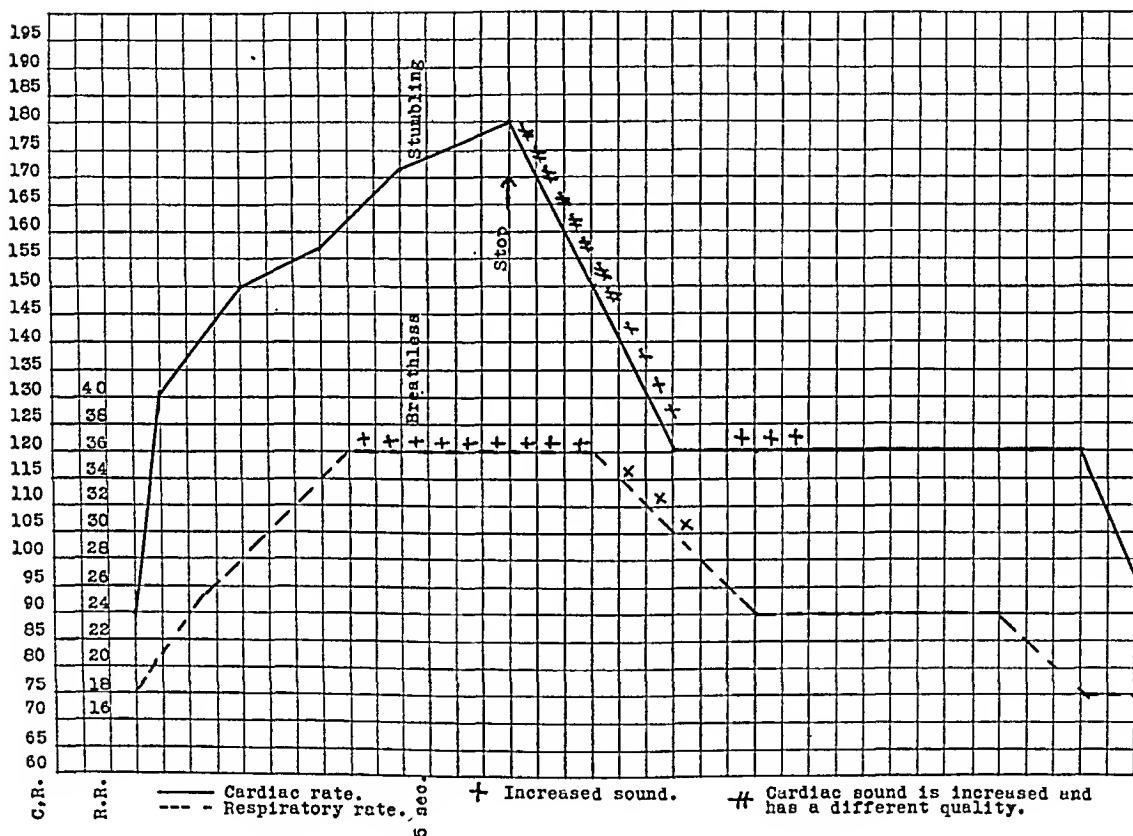


CHART 11. A bad test in a vagohypotonic individual.

beats per minute. We know that it is the vagus action because atropine abolishes it.

The onset of Starling's cycle is indicated by a suddenly marked increase in the cardiac first sound and sometimes a change in quality of sound, as well.

After the individual becomes exhausted and is allowed to rest, then there is another immediate rise in rate, reaching its maximum within five seconds of time.

In untrained individuals this can be a rise of from 30 to 50 beats per minute. In the trained individual, this rise is usually from 10 to 30 beats per minute. Unless the heart is definitely fatigued this increase in rate may not be present. The rise in rate is brought about by the sudden ceasing of the working of Marey's Law, that is, it is brought about by the sudden drop in blood pressure in the aorta and carotid sinus, allowing the accelerator influences free play. The vagus now slowly regains its tone, and from the highest point the rate slowly drops, reaching a normal rate from 60 to 80 seconds after the cessation of exercise.

Arthur D. After $\frac{1}{100}$ gr. atropine sulphate—hypo.

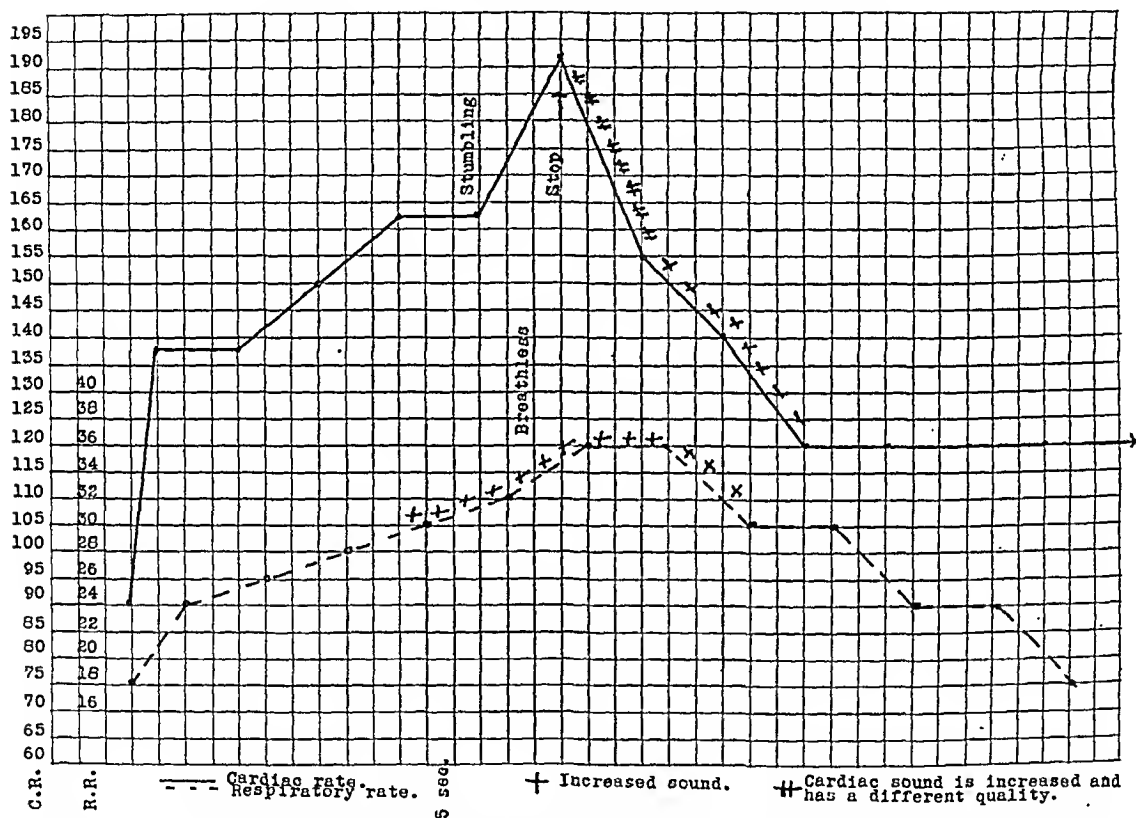


CHART 12. No. 11 after the administration of atropine. Note how little change atropine produces, due to the fact there is but little vagus control to be lost.

This description covers the reaction of the heart to work in the normal individual. We have encountered three types of individuals, however, that do not respond in this way to exercise.

First is the *vagohypotonic* individual. Vagus tone is essentially of a protective nature and its development depends greatly upon the requirements of the individual. In some individuals this protective tone of the vagus (although there is some doubt that the vagus alone is involved) is below par, and this autonomic imbalance is the cause of many functional disturbances that are grouped together under the symptom complex of vago-

hypotonia. The vagohypotonic individual has no normal resting cardiac rate; it may be anywhere between 90 and 110.

In the vagohypotonic individual, with the beginning of exercise, the cardiac rate responds to the Bainbridge reflex, and at the point where it should meet the vagus control, i.e., 120 beats per minute, there is no check upon its velocity, and it increases to an exceedingly high rate, causing the individual quickly to become exhausted. On rest, this individual does not have the rise in rate which in the normal individual comes with the release of the vagus from the stimulation of the distended aorta and carotid sinus, but that control being absent and the rate having risen to an uncontrolled

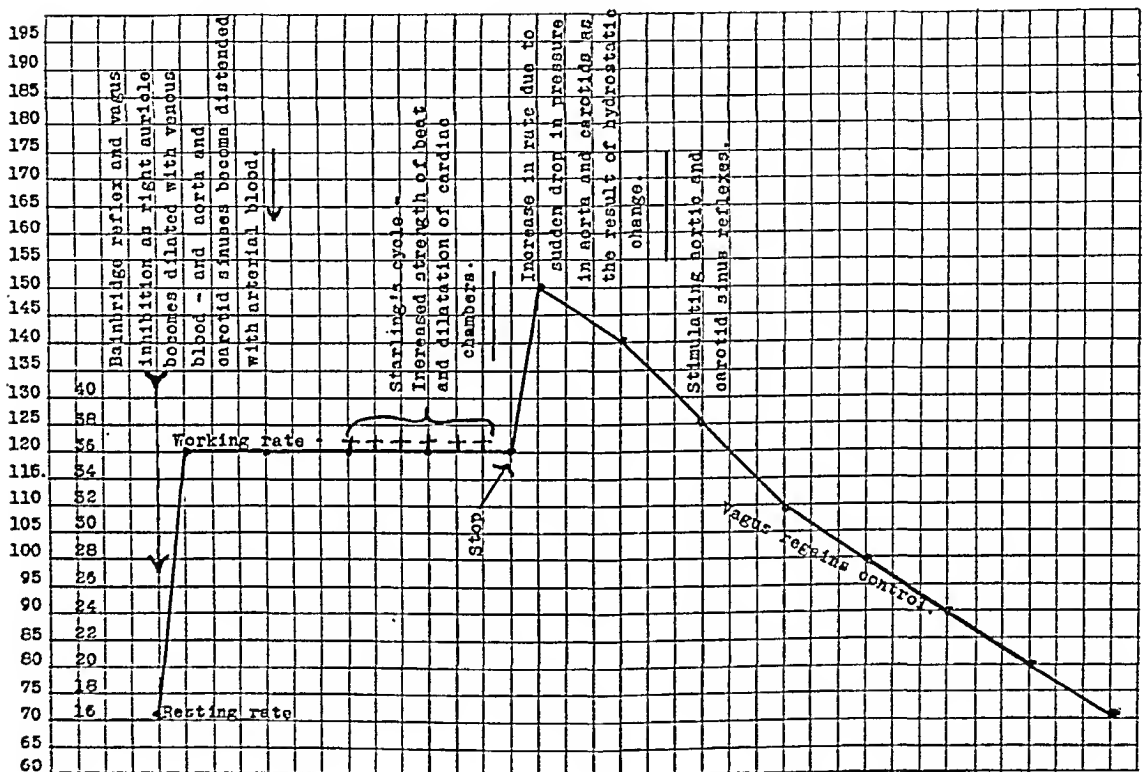


CHART 13. Possible physiological explanation of normal record.

level (sometimes as high as 240 beats per minute), the rate starts dropping from its highest point at the ceasing of exercise. However, when the slowly dropping rate reaches 120 beats per minute it is held on a plateau at this level for an indefinite length of time, evidently allowing for certain readjustments in the circulation and within the heart itself, probably made necessary by the extreme rate. After the pulse has been held at this plateau of 120 beats (which we designate the plateau of rest and which strangely coincides with the plateau of the working rate of the heart), from 30 to 80 seconds or more, it slowly seeks its previous resting rate. The administration of atropine has no effect on the test of a vagohypotonic individual.

The second type of individual that does not respond normally to exercise is the individual with a myocardium so damaged that there is no longer a normal conductivity of impulses through it. The reaction in cardiac rate in this type of individual to cardiac fatigue is exactly the same as that of the vagohypotonic individual, including the plateau of rest during the period of recovery, at 120 beats per minute.

The third type of individual that does not respond normally to exercise is the individual with valvular defects. When these defects are well compensated for and can maintain a normal circulatory response to exercise, the heart gives a perfectly normal test; whereas individuals with poorly compensated valvular defects, who, in spite of their increased rate on exercise, cannot maintain an increased output (for an acceleration of the pulse rate does not indicate an increased cardiac output, but may indicate merely a demand for such an increase), give an abnormal test. There is a lack of increased intra-arterial pressure in the aorta and carotids, due to a faulty cardiac output, so that no vagus control is initiated to establish a normal working level of the pulse. In many cases this is probably aided by damaged conductivity of the heart muscle. The rate continues to increase until the individual is exhausted and then drops as in the other two instances, again establishing a plateau of rest at 120 beats per minute, allowing the heart and circulation to readjust themselves after having maintained an excessive cardiac rate.

The important elements in the graphic charting of the cardiac rates maintained by the heart during exercise are:

The ability of the heart to maintain a normal plateau of working rate at 120 beats a minute.

The ability of the heart promptly to increase its rate on rest and then as promptly to decrease this rate.

A plateau during the resting period indicates poor cardiac function and the degree of disability is indicated by the length of time this plateau is maintained.

We are fully aware that this test is a crude method of measuring the cardiac events described above and that instruments of precision applied to the test may show that the graphs do not run so smoothly, but the test is simple and easily done (this is essential in examining large groups), and is, in the main, accurate in its demonstration of the heart's ability to function properly.

This year we have examined 100 athletes carrying out the complete cardiac examination. Seventeen hearts were found to exceed their predicted transverse diameter. Sixteen of these showed evidence of cardiac damage on physical examination or electrocardiographic examination, or both. The remaining one showed marked evidence of vagohypotonia. Of the 17 with cardiac enlargement, 12 gave a function test that was poor or bad, while five gave function tests that could be graded from fair to good.

Among the 83 athletes with hearts within the predicted measurements, 80 gave tests rating from fair to good, while three (all showing evidence of vagohypotonia) were rated poor.

CONCLUSIONS

We feel that the presence of cardiac hypertrophy in a group of athletes points to the ineffectiveness of the cardiac examination given the athletes.

A complete examination of the heart is expensive and time-consuming, and requires an especially trained personnel.

We feel that the function test described above will allow an examiner to appreciate the heart's reaction to physical exertion by its changes in rate, and by the changes in the sounds produced by its contractions.

BIBLIOGRAPHY

1. WILLIAMSON, C. S.: The effect of exercise on the normal and pathological heart, *Am. Jr. Med. Sci.*, 1909, cxxxviii, 549.
2. SHATTUCK, G. C.: Cardiac enlargement, *Boston Med. and Surg. Jr.*, 1916, clxxiv, 384.
3. JOSEPHS, D. R.: Ratio between the heart weight and body weight in various animals, *Jr. Exper. Med.*, 1908, x, 521.
4. DEUTSCH, F., and KAUF, E.: Heart and athletics (Translation by L. M. Warfield), 1927, C. V. Mosby Co., St. Louis, Mo.
5. EYSTER, J. A. E.: Determination of cardiac hypertrophy by roentgen-ray methods, *Arch. Int. Med.*, 1928, xli, 667.
6. HODGES, FRED J., and EYSTER, J. A. E.: Estimation of transverse cardiac diameter in man, *Arch. Int. Med.*, 1926, xxxvii, 707.
7. PEABODY, F. W.: Vital capacity of lungs in heart disease, *Med. Clin. N. Am.*, 1921, iv, 1655.
8. BLUMER, GEORGE: Bedside diagnosis, Vol. II, 1928, W. B. Saunders, Philadelphia, p. 545.
9. SMITH, H. L.: "Athletic heart," an unfortunate term, *Proc. Staff Meet. Mayo Clin.*, 1935, x, 122.
10. WHITE, S. A., and MCGUIRE, P.: Vital capacity in citizens' military training camp, *Arch. Int. Med.*, 1925, xxxvi, 355-365.
11. PEACOCK, T. B.: On some of the causes and effects of valvular disease of the heart, 1865, J. Churchill and Sons, London.
12. DA COSTA, J. C.: Physical diagnosis, 1916, W. B. Saunders, Philadelphia.
13. BEDFORD, EVAN D.: The size of the healthy heart and its measurement, *Lancet*, 1931, ii, 836.
14. MESSINGER, E.: The estimation of cardiac function by simple clinical methods, *Ann. Int. Med.*, 1937, x, 986.
15. WHITE, P. D.: Heart disease, Macmillan Company, New York, pp. 454-479.
16. CABOT, RICHARD: Facts on the heart, 1926, W. B. Saunders, Philadelphia.
17. WOOD, J. E., and WHITE, P. D.: Interpretation of mitral diastolic and aortic systolic murmurs, *Med. Clin. N. Am.*, 1923, vii, 729.
18. HELD, E., GOLDBLOOM, A. A., and RITTENBERG, L. M.: Mitral stenosis with special reference to buttonhole mitral stenosis, *Med. Clin. N. Am.*, 1931, xiv, 1311.
19. PATERSON, R., and PATERSON, E.: Experiment on the effect of exercise on the heart in athletes, *Am. Jr. Roentgenol.*, 1935, xxxiv, 158.
20. LEVENE, G., and REID, W. D.: A chart for the differential diagnosis of cardiac enlargement by means of roentgen ray, *Am. Heart Jr.*, 1931, vii, 380.

21. EYSTER, J. A. E.: The size of the heart in normal and in organic disease, *Radiology*, 1927, viii, 300-306.
22. GOLDEN, R.: Diagnostic roentgenology—measurement of the cardiovascular system, 1938, Thomas Nelson and Sons, N. Y., p. 209.
23. DANZER, C. S.: The cardi thoracic ratio, an index of cardiac enlargement, *Am. Jr. Med. Sci.*, 1919, elvii, 513.
24. BARDEEN, C. R.: Determination of the size of the heart by means of the x-rays, *Am. Jr. Anat.*, 1918, xxiii, 423.
25. STEINHAUS, A. H.: Chronic effects of exercise, *Physiol. Rev.*, 1933, xiii, 103.
26. BAIN TON, J. H.: Silhouette of the heart and the aortic arch, *Am. Heart Jr.*, 1932, viii, 616.
27. STEINHAUS, A. H., KIRMIZ, J. P., and LAURITSEN, K.: Studies in the physiology of exercise; chronic effects of running and swimming on hearts of growing dogs as revealed by roentgenography, *Am. Jr. Physiol.*, 1932, xcix, 487.
28. HERRMANN, G. R.: The heart of the racing greyhound, *Proc. Soc. Exper. Biol. and Med.*, 1926, xxiii, 856.
29. ROESLER, HUGO: A roentgenological study of the heart size in athletes, *Am. Jr. Roentgenol.*, 1936, xxxvi, 849.
30. ANREP, G. V.: Lane medical lectures: Studies in cardiovascular regulation, 1936, Stanford University Press.
31. HEYMANS, C., and LADON, A.: Recherches physiologiques et pharmacologiques sur la tête isolée et le centre vague du chien, *Arch. internat. de pharmacod.*, 1925, xxx, 415.
32. HERING, H. E.: Compression of carotid artery, *München. med. Wchnsehr.*, 1923, vii, 1287. Die Karotissinusreflexe auf Herz und Gefäße, 1927, Theodor Steinkopff, Dresden.
33. HEYMANS, C.: *Arch. internat. de pharmacod.*, 1929, xxxv, 269.
34. BOWEN, W. P.: Changes in heart rate, blood pressure, and duration of systole resulting from bicycling, *Am. Jr. Physiol.*, 1904, xi, 59.
35. FRANK, OTTO: Zur Dynamik des Herzmuskels, *Ztschr. f. Biol.*, 1895, xxxii, 370.
36. GROLLMAN, ARTHUR: The cardiac output of man in health and disease, 1932, Charles C. Thomas, Springfield, Illinois.
37. WIGGERS, C. J.: Physiology in health and disease, 1937, Lea and Febiger, Philadelphia.
38. HEWLETT, A. W.: Pathological physiology of internal diseases, 1924, D. Appleton and Company, New York.
39. McDOWALL, R. J. S.: Clinical physiology, 1927, D. Appleton and Company, New York.
40. McDOWALL, R. J. S.: A vago-pressor reflex, *Jr. Physiol.*, 1924-25, lix, 41.
41. MACWILLIAM, J. A.: On the influence exercised by the central nervous system on the cardiac rhythm with an inquiry into the action of chloroform on that rhythm, *Proc. Roy. Soc.*, 1893, liii, 465.
42. NEWBURGH, L. H., and MEANS, J. H.: The blood flow in a patient with double aortic and double mitral disease, *Jr. Pharmacol. and Exper. Therap.*, 1915, vii, 441.
43. MEEK, W. J., and EYSTER, J. A. E.: Cardiac size and output in man during rest and moderate exercise, *Am. Jr. Physiol.*, 1922, lxiii, 400.
44. BAINBRIDGE, F. A.: The influence of venous filling upon the rate of the heart, *Jr. Physiol.*, 1915-16, 1, 65.
45. GASSER, H. S., and MEEK, W. J.: A study of the mechanisms by which muscular exercise produces acceleration of the heart, *Am. Jr. Physiol.*, 1914, xxxiv, 49.
46. McDOWALL, R. J. S.: A right auricular pressor reflex, *Jr. Physiol.*, 1934, lxxxi, 5.
47. McDOWALL, R. J. S.: Nervous control of blood vessels, *Physiol. Rev.*, 1935, xv, 98.
48. HERING, H. E.: Ueber die Beziehung der extracardialen Herznerven zur Steigerung der Herzschlagzahl bei Muskelthätigkeit, *Arch. f. d. ges. Physiol.*, 1895, ix, 429.
49. HEYMANS, C., and LADON, A.³¹
50. MANSFELD, G.: Die Ursache der motorischen Acceleration des Herzens, *Arch. f. d. ges. Physiol.*, 1910, cxxxiv, 598.

51. LEWIS, SIR THOMAS: Diseases of the heart described for practitioners and students, 1937, Macmillan Company, London.
52. CHRISTIAN, H. A.: The diagnosis and treatment of diseases of the heart, 1935, Oxford University Press, London.
53. PATTERSON, S. W., PIPER, H., and STARLING, E. H.: Jr. *Physiol.*, 1914, xlviii, 465.
54. STARLING, E. H.: Harveian Oration: Wisdom of the body, *Lancet*, 1923, ii, 865.
55. STINE, D. G.: The meaning of athletic heart among university athletes, Proceedings of the eighteenth annual meeting of the American Student Health Association, December, 1937, Chicago.
56. STINE, D. G.: The effect of work upon the heart, Jr. Missouri State Med. Assoc., 1938, xxxv, 443-446.

ROENTGEN PROCEDURES USEFUL IN CARDIAC DIAGNOSIS *

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BLUNTLY stated, the medical profession's ability to diagnose diseases of the heart greatly outweighs its ability to successfully treat patients with cardiac disorders. This discrepancy has served as a stimulus to even further development in the field of cardiac diagnosis based upon the belief that rational and successful therapeutic efforts can be developed only upon a broader and more complete understanding of the subject.

Roentgen-rays, because of their unique ability to penetrate successfully the various tissues of the body, offer a means of observing the heart which has appealed to physicians ever since the year of Roentgen's discovery. In common with progressive development in electrocardiography, new adaptations of the roentgen-ray method to the study of heart disease have been described from year to year, until in the aggregate there has developed a considerable literature devoted to this particular subject. It is difficult to evaluate rigidly the importance of individual procedures since the efficacy of these varies greatly, depending upon the type of cardiac abnormality under consideration. Roentgen-ray examination alone, however specific and detailed, never constitutes adequate study in any individual case, although it may on occasion be more helpful than any other single procedure.

It is wise to remember that under some circumstances, which unfortunately are not uncommonly encountered in patients with cardiac disease, all roentgen-ray methods of study may be rendered entirely ineffectual. If the heart is surrounded by accumulations of pleural fluid, or lung rendered abnormally dense as the result of disease, or if its roentgen shadow is obscured because of abnormal elevation of the diaphragm, shift of the mediastinum, vertebral deformity, great adiposity, herniation of abdominal structures through the diaphragm, or other comparable situations it is obviously impossible for roentgen procedures to succeed. Certain diagnostic procedures depending upon the use of roentgen-rays require a degree of cooperation on the part of the subject being examined which the patient's condition may not permit. Some of the more elaborate procedures require, in addition to wide experience and great ingenuity on the part of the examiner, highly specialized equipment, which it is impracticable to maintain in any roentgen laboratory where the demands for highly specialized cardiac examination are infrequent. Some of the more uncommonly employed methods of studying the heart require a great deal of time and effort on the part of the examiner, and may be properly considered experimental rather than clinically practicable investigations. An opportunity to observe casually

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the shadow cast by the heart and its great vessels as shown in a simple roentgenogram of the chest in frontal projection is satisfying to the cardiologist, if nothing more, for many of the observations he is able to make without such assistance are less rapid and more indirect. Good judgment is required in order to determine which patients can be advantageously studied with roentgen-ray methods of a more highly specialized nature. Such decisions depend to a very large extent upon findings observed in a preliminary survey of the entire chest, although many other indications are to be found in the patient's history and among findings obtained on searching physical examination.

PRELIMINARY SCOUT ROENTGENOGRAM OF CHEST

Situations responsible for insurmountable technical difficulties certain to defeat accurate roentgen-ray examination of the heart are readily detected by cursory inspection of a scout film. Figures 1 and 2 represent circum-

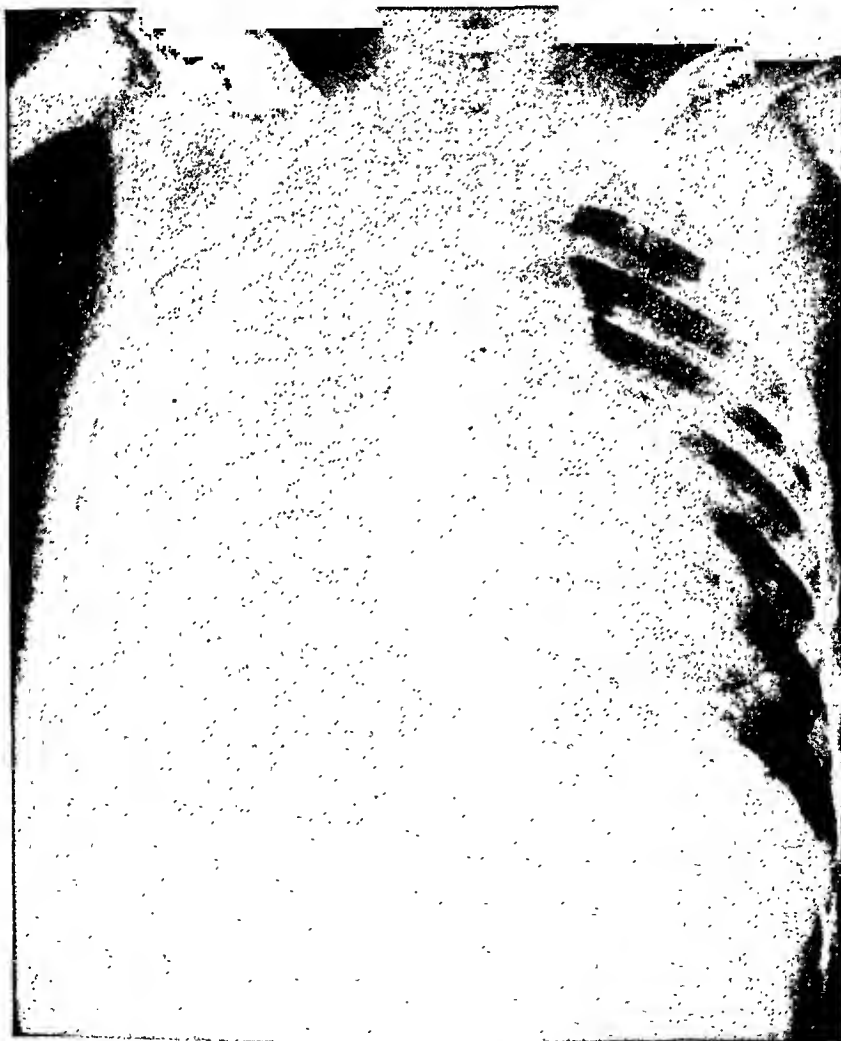


FIG. 1. Massive pleural effusion obliterating right cardiac border.

stances which operate to render the shadow of the heart indistinguishable from surrounding structures. In the first of these the entire right chest has been rendered uniformly opaque by the accumulation of pleural fluid, whereas in the second example chronic obstruction of the main bronchus on the left followed by pulmonary atelectasis and an extreme degree of bronchiectasis serves to conceal the heart which has been displaced sharply to the



FIG. 2. Obstruction of the left bronchus producing bronchiectasis, atelectasis, and mediastinal shift to the left with resultant obliteration of cardiac contours.

affected side as the result of compensatory emphysema in the contralateral lung. Figure 3 shows a very obviously enlarged cardiac shadow. In this instance it would seem wise to determine, with whatever degree of accuracy is possible, the extent to which this patient's heart has been enlarged. In figures 4 and 5, the contours of the heart are seen at first glance to deviate materially from the expected shape of the cardiac silhouette. Remarkable

bilateral broadening of the shadow just above the diaphragm, and obvious total enlargement of the shadow, at once suggest the likelihood of underlying pericarditis with effusion; a point which might be subjected to further clarification by additional fluoroscopic and roentgenographic study. In figure 5 the abnormality in shape suggests a congenital malformation which might well be profitably studied by far more elaborate examination by roentgen methods.

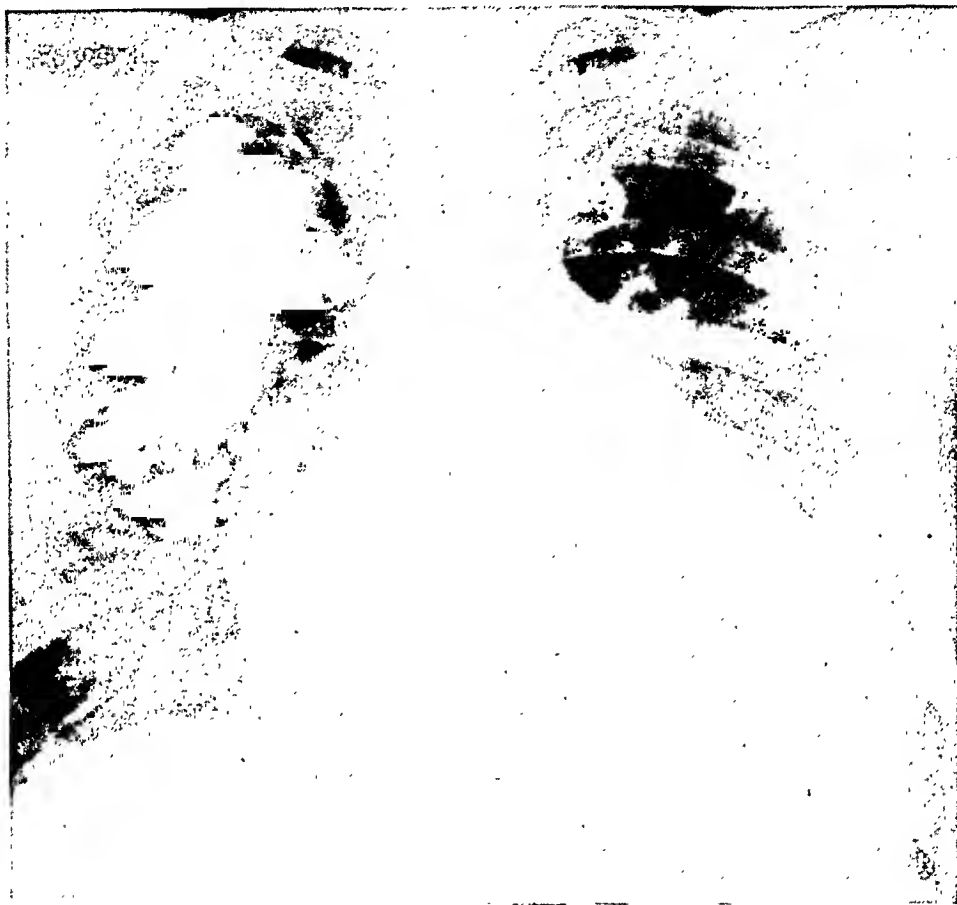


FIG. 3. Marked cardiac enlargement.

These few illustrations will serve to show how a single scout film of the chest may quickly convince the examiner that further roentgen-ray study of the heart in a given case is apt to be profitless, or on the other hand stimulate him to employ further, more detailed, roentgen procedures.

CARDIAC SIZE AND VOLUME DETERMINATION

Without doubt the most commonly employed and withal the most generally profitable utilization of roentgen-rays in the study of the heart is directed toward the measurement of cardiac size. Heart size determination, comparable in accuracy to anthropological standards, is impossible even

under the most favorable conditions. A number of schemes have been proposed, however, whereby estimations of heart size may be derived from roentgen-ray measurements for comparison with computed normal values. These have met with varying degrees of favor in clinical practice. These methods group themselves into three general types: those which depend upon the value of one or more cardiac diameters, those based upon cardiac area measurement, and those which seek to express heart size in terms of volume. Measurements in terms of diameter have been in the past and are today more widely used in clinical practice than area and volume determinations which



FIG. 4. Abnormal cardiac shape: pericardial effusion.

require somewhat more effort on the part of the examiner and, in some cases, highly particularized roentgenological study. If the heart were a regular and symmetrical solid, determination of one or more characteristic diameters or the area of certain sectional planes would serve perfectly well as a basis for computing volume. Since the heart is not a regular geometrical figure, measurements of this sort can be expected to yield only approximate values for volume. Direct measurement of silhouette area involves smaller inherent error than diameter measurement since deviations from regular spherical or ovoid curvature can be directly measured, at least

in those planes selected for area determination. The most direct method of volume determination as yet devised and proposed consists of reconstruction of the heart in plastic material by modeling the silhouette contours in successive stages of axial rotation. This can be done and as a matter of fact a modified, somewhat less awkward and less time consuming scheme is entirely practicable in those cases where highly accurate volume determination is sufficiently valuable to warrant the necessary effort.

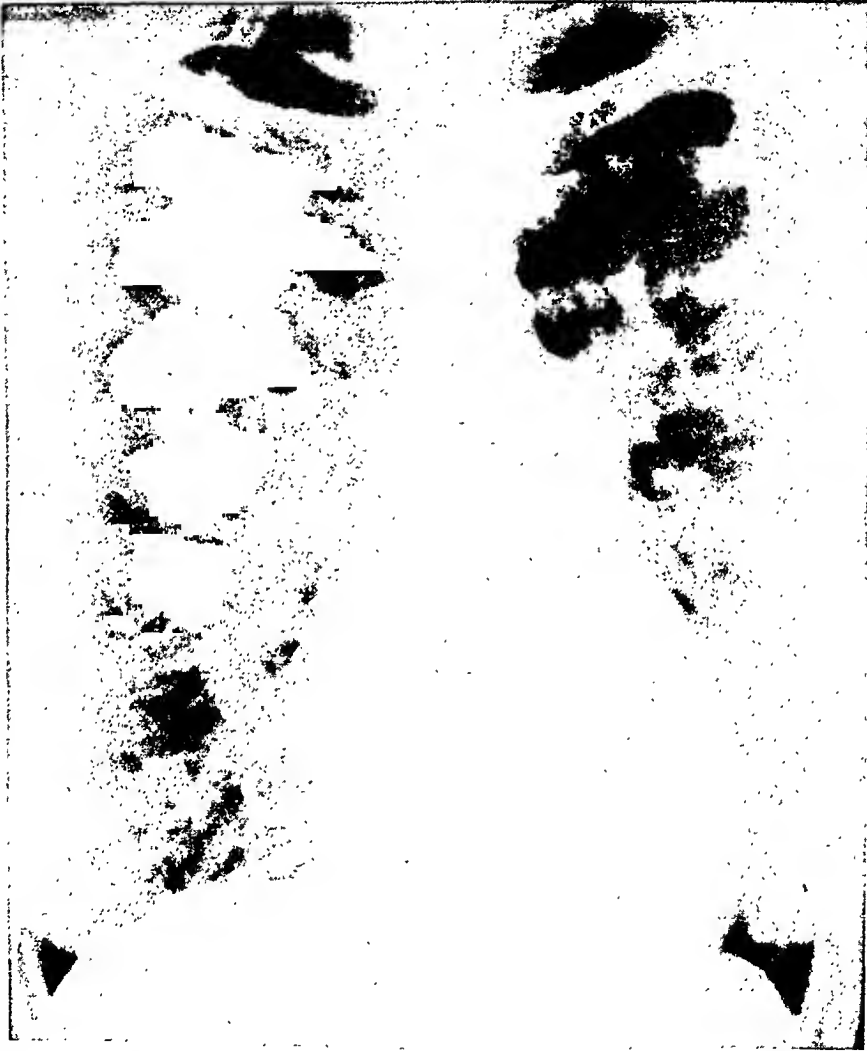


FIG. 5. Congenital heart disease: hypoplasia of aorta, patent foramen ovale.

Area measurements are obtainable with much less difficulty and a fair degree of accuracy by employing a draftsman's planimeter which expresses the silhouette perimeter in units of area. In some clinics a number of diameters are measured and reported as direct values or in the form of comparative indices with some other body measurement. The most commonly employed of these is the well-known Danzer ratio, which relates total trans-

verse diameter of the heart with total transverse diameter of the thorax. Actually this particular ratio is a relatively crude index of cardiac size which, if used, should be considered subject to wide limits of error.

Numerous variations of the three basic methods mentioned, as well as combinations of diameter and area measurements, have been proposed. The most extensive efforts to establish reliable normal values against which individual measurements may be compared are based upon frontal silhouette area and greatest transverse diameter determinations. Since area can be measured with reasonable accuracy, either by the employment of orthodiascopy or the measurement of corrected frontal plane silhouettes obtained radiographically, the adoption of this plan seems advisable.

Figure 6 shows the more commonly used cardiac diameters, the portion of a frontal plane cardiac silhouette ordinarily employed in area determination, and the manner in which an orthodiagraphic tracing can be similarly employed, as well as one plan of measurement based upon diameters obtainable only in the left anterior oblique projection. This diagram is taken from the record of a single patient and the values shown clearly indicate the variability to be expected when different methods of measurement are employed.

If one is willing to make necessary allowances for inherent errors known to exist in all methods of estimating cardiac size, numerical values may be very helpful in expressing various degrees of cardiac enlargement. It is often gratifying to be able to express progressive cardiac enlargement over a period of time in this fashion. The roentgenologist should constantly remind himself, as well as the physicians who refer cardiac patients to him for study, that numerical expressions of cardiac size are accurate only to a degree.

Figure 7, representing three interval examinations, shows very obvious progressive enlargement. Numerical expressions of heart size in terms of percentage variation from the expected normal as computed from age, height, and body weight, are very expressive of the changes recognizable roentgenographically and have the advantage of being easily transferred to the patient's case record in readable form.

SIGNIFICANCE OF ALTERATION OF CARDIAC SHAPE

No rigidly defined normal cardiac silhouette shape can be described in comparison with which all other shapes may be considered definitely pathological. This is true because in addition to individual variations comparable to those which occur in other parts of the body, the heart is readily affected in the matter of position and shape referable to body habitus as well as abnormalities affecting the vertebral column, the ribs and sternum, the lungs, the diaphragm and extra-cardiac structures which occupy the mediastinal space. Before ascribing any significant importance to apparent variations in shape, all of these possibilities must be carefully evaluated.

Cardiologists and roentgenologists, trained and experienced in such matters, are able with a reasonable degree of success to recognize, classify, and evaluate contour changes expressing anatomical alterations limited to or predominant in one or more chambers of the heart. Attempts on the part of

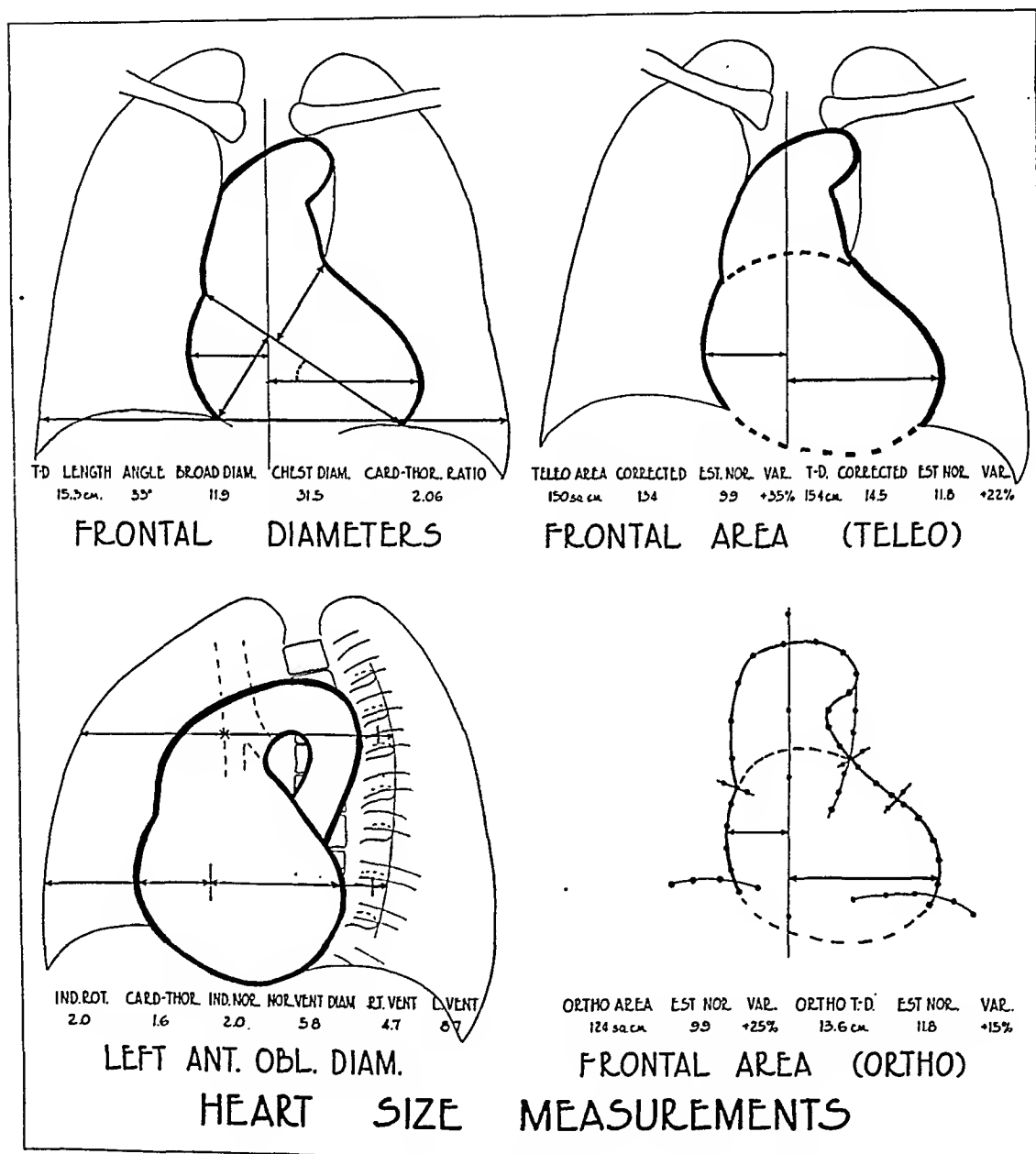


FIG. 6. Commonly employed diameter and area measurements.

unskilled observers to recognize the existence of various valvular lesions on the basis of such evidence are harmful since they create the false impression that changes in cardiac shape readily and accurately reflect specific valvular defects. Compared with evidences of cardiac enlargement, which should

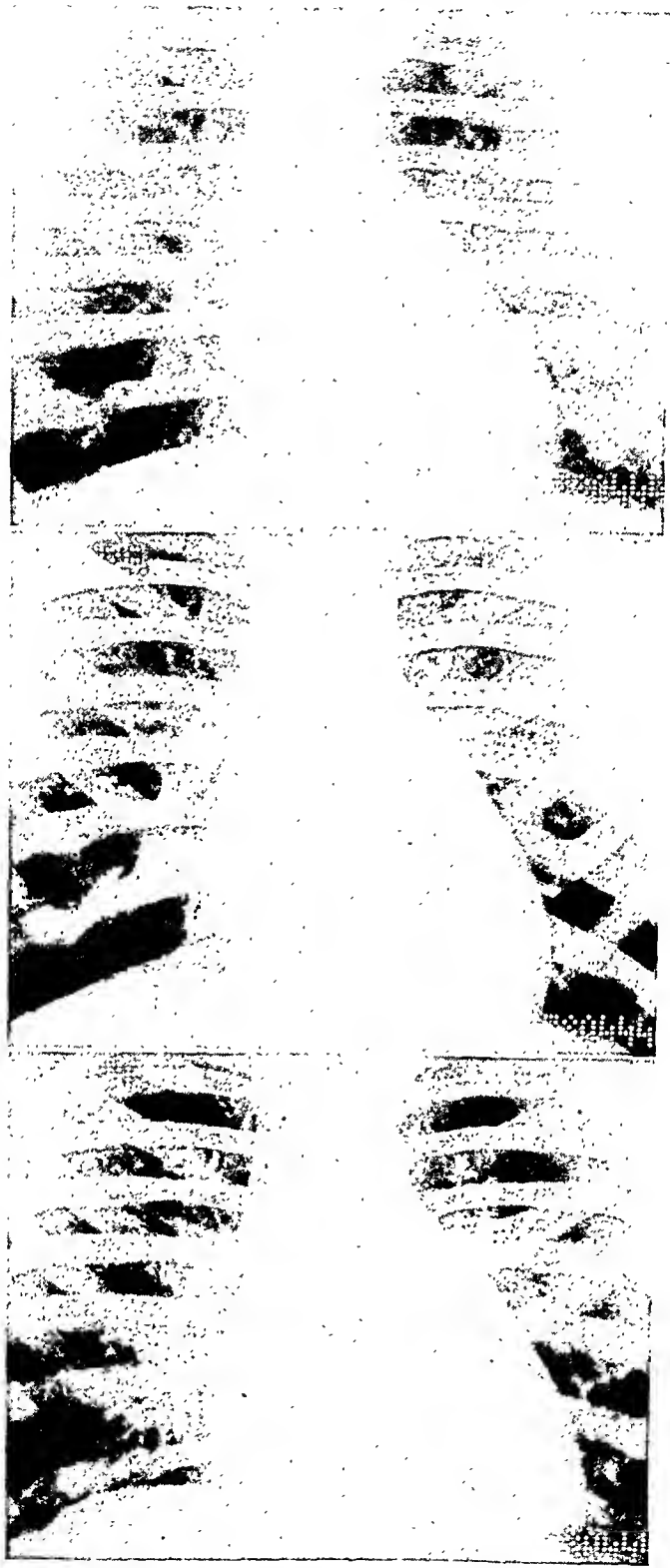


FIG. 7. Progressive enlargement of cardiac silhouette. +12% +32% +49%

never occur in the absence of underlying disease, cardiac shape must be considered a far less reliable criterion of significant abnormality.

Certain variations in shape are more or less characteristic of some of the congenital anomalies involving the heart and great vessels. Considered from the point of view of the roentgenologist, the relatively accessible location of the left auricle, and the frequency with which changes in its size and shape are associated with narrowing of the mitral ring, render conditions in which stenosis of this particular valve is a feature, readily susceptible to identification by the roentgen method. Similar enlargement of the left ventricle associated with stenosis or insufficiency of the aortic valve, though recognizable in many instances, is far less uniformly detectable. In figure 8 are reproduced frontal and lateral roentgenograms showing unmistakable signs of left auricular enlargement. All other types of examination serve to confirm the diagnosis of well established mitral stenosis in this patient. The characteristic features are unusual prominence and sharp convexity along the upper portion of the left cardiac contour, the zone in which one would expect to find evidence of left auricular enlargement, and localized obliteration of the normally transparent retrocardiac space corresponding to the posterior location of this chamber. Enlargement of the heart shadow downward and to the left, without evidence of corresponding enlargement to the right of the mid line, or in the left auricular zone, bespeaks enlargement primarily limited to the left ventricle. Such findings are shown in figure 9. In this patient the diagnosis of aortic stenosis has been established clinically.

ROENTGENOLOGICAL SIGNS OF PERICARDIAL EFFUSION

The presence of excessive amounts of fluid within the pericardial space offers many diagnostic difficulties for the roentgenologist, in spite of the fact that one might well expect this situation to lend itself remarkably well to his methods of study. In the early stages of the disease, pericarditis may be easily recognizable on the basis of suddenly developing friction rub without corresponding characteristic signs detectable roentgenologically. The heart may, of course, be enlarged and often is, but that is no reliable criterion of impending pericardial effusion. Once fluid develops, the most obvious effect is further enlargement of the cardiac silhouette. The density of the heart being almost exactly the same as that of normal and pathological body fluids, it is impossible to visualize the borders of the heart itself within the outlines of the distended pericardium. To a certain extent only may the presence of fluid be reliably detected by alterations in the contour of the heart shadow. These are not difficult to appreciate as a rule if the patient has been examined on repeated occasions. It is surprising, however, how often relative broadening at the base of the cardiac shadow and increased acuity of the angles formed by the diaphragm and the lateral borders of the heart fail to provide conclusive evidence even in well established cases of pericardial



FIG. 8. Left auricular enlargement. Mitral stenosis.

effusion. By resorting to the use of the fluoroscope, one can recognize feeble pulsations of the shadow contours and examination of the patient, first in the upright, then in the horizontal position, will sometimes show suggestive or even characteristic alterations in the breadth of the cardiac shadow. Roentgen-ray examination may be very helpful as an adjunct to other methods of study, and may even on occasion be the first agency to discover signs suggesting this situation, but unrecognized instances of pericardial effusion, as well as occasions when this situation is erroneously reported, serve to emphasize the fallibility of roentgen signs in this disease.



FIG. 9. Predominant enlargement of the left ventricle.

When, because of the overwhelming clinical evidences of pericardial effusion, aspiration is carried out and followed by the injection of small amounts of air, cardiac roentgenograms are as a rule very startling in appearance. Reëxamination from time to time is a helpful means of determining the rate at which fluid is being re-formed, and sometimes the progressive development of intra-pericardial adhesions can be observed. Figure

10 is reproduced from films in a case of pyo-pericardium at the height of the disease and also after complete recovery following surgical drainage. Figure 11 illustrates the appearance which may be observed after fluid aspiration and the re-injection of air.

THE DEMONSTRATION OF ABNORMAL OPACITIES WITHIN THE HEART AND PERICARDIUM

The deposition of lime salt in the pericardium, the epicardium, and the loose connective tissues which surround the superficial coronary vessels constitutes an important contribution to the diagnosis of pericardial disease. When such depositions can be clearly demonstrated, even though the amount of calcium may be small, their presence constitutes proof positive of pre-existing inflammatory disease. When these deposits are massive, as is sometimes the case, roentgenographic findings are startling. To demonstrate such findings, lateral and oblique projections are the most desirable, although in the case of the smaller deposits the optimum angle of projection is best determined in advance fluoroscopically. Calcium deposits are seen to best advantage in roentgenograms prepared with the use of a Potter-Bucky diaphragm, or some other type of grid or lattice to enhance contrast. Figure 12 represents an example of extensive calcium deposition about coronary vessels associated with constrictive pericarditis in this particular instance.

Occasionally inspection of a chest roentgenogram will show single or clustered shadows of great density centrally placed within the cardiac silhouette, which represent lime salt deposition within the annulus fibrosus or within the leaflets of cardiac valves. Much more commonly such calcium deposits can be recognized fluoroscopically, although it is necessary to employ every available mechanical advantage in order to do so. With his eyes thoroughly accustomed to darkness, the operator must employ a very small beam of roentgen-rays of relatively high intensity, the most efficient fluoroscopic screen available, and no little ingenuity in the matter of advantageously rotating his patient in order to detect the presence of such shadows. Valve shadows, of course, are always projected within the contours of the heart, no matter what position is employed. When observed, calcified valves can be identified by their characteristic dancing motion. Aortic valve calcification in a case of aortic stenosis and regurgitation is shown in figure 13. The results of such observations have shown that the mitral valve is located somewhat more posteriorly and nearer to the cardiac apex than the aortic valve. Exceedingly rapid exposures are necessary to record correctly the shadows of valve calcification. Calcium deposition in either the annulus fibrosus or the valves themselves proves conclusively the existence of chronic inflammatory or degenerative disease.

Occasionally the roentgenologist is called upon to examine patients harboring opaque foreign bodies within the heart or in its immediate vicinity. Each situation of this sort offers its own problem and its own diagnostic

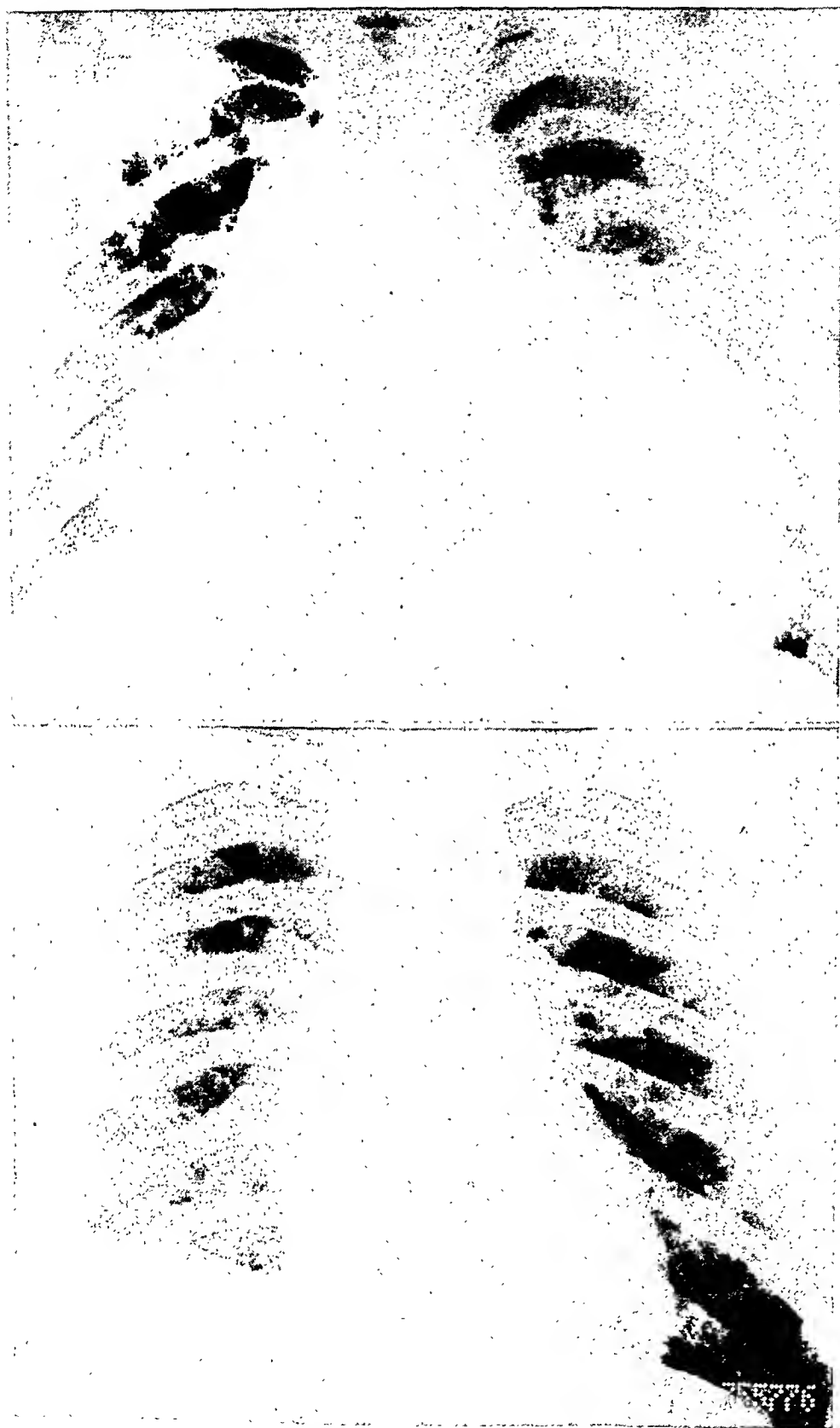


FIG. 10. Pyopericardium before and after surgical drainage.

reward. Occasionally metallic foreign bodies have been described within the chambers of the heart where they have been observed to reflect movements of the blood and the contractions of the cardiac wall. Sometimes fragments of bullets, broken knife blades, portions of aspiration needles, and other metallic fragments have been observed to lie within the pericardial cavity or actually imbedded within the muscle of the heart. It is obvious that if surgical removal of such objects is contemplated, preliminary localization with respect to cardiac landmarks is desirable and altogether feasible.



FIG. 11. Hydro-pneumopericardium.

THE STUDY OF CARDIAC MOVEMENTS

Movements of the cardiac borders can be studied with a considerable degree of accuracy by means of a number of modifications of the roentgenological method. Film may be moved at slow or fast speed behind a lead screen provided with a slit to record movements of a given point on the contour of the heart, thus providing a continuous record of the motion at this point throughout one or more cycles. If the motion applied to the film is of relatively short amplitude, a number of apertures can be arranged permitting the simultaneous study of the motion of the cardiac contour at a number of different points. Simultaneous recording of the electrocardiogram, venous and carotid pulse tracings, and amplified heart sounds give to



FIG. 12. Extensive pericardial calcification.

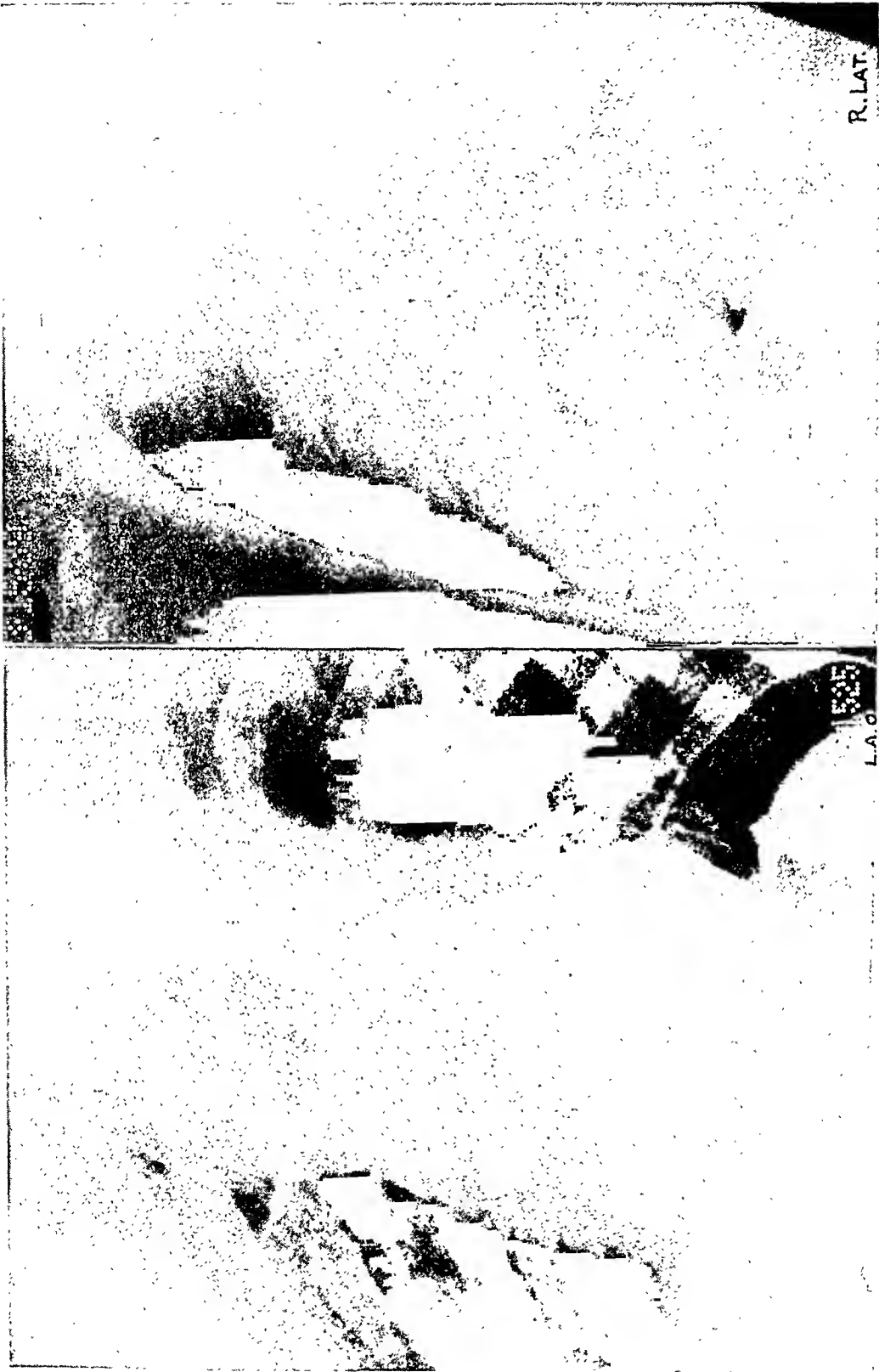


FIG. 13. Male, aged 33. Clinical signs of aortic regurgitation. Visible calcification in aortic valve leaflets.

the examiner a rich fund of accurate information regarding the behavior of the heart if intensive study of this sort is desired.

In actual clinical practice this method of study known as roentgen kymography is restricted for the most part to its employment for the purpose of identifying, on the basis of characteristic motion, certain segments of the cardiac contour in various projections which may for one reason or another appear to offer diagnostic possibilities. For example, one may want to know whether unusual prominence or fullness high on the left cardiac margin represents marked enlargement of the left auricle or bulging at the base of the left ventricle. As a rule this question can be answered quickly by simple fluoroscopic observation, but when the amplitude of pulsation is very short kymographic examination may be the only reliable means of making this determination. Direct comparison with a point of known identity quickly and positively identifies movement as auricular or ventricular in phase. The roentgen kymograph is also very serviceable in detecting and identifying the nature of pulsation in abnormal mediastinal masses. The recognition of non-pulsating segments along the ventricular contours is also rendered feasible and positive by this method of study.

Movements of the heart which are related to the phases of respiration can be observed quite readily on direct fluoroscopy and may be very enlightening in the interpretation of cardiac roentgenograms. On occasions movements of rotation and pulsation are transmitted from the heart to abnormal intrathoracic masses in such a manner as to greatly modify their roentgenological appearance. Sometimes such transmitted movements may very closely simulate intrinsic expansile pulsation even in the case of solid mediastinal and pulmonary tumors.

THE STUDY OF BLOOD FLOW THROUGH CARDIAC CHAMBERS

If it were true that a distinct difference in density existed between heart muscle and blood under normal conditions, the physiology of cardiac circulation might be studied to excellent advantage by the employment of roentgenological methods of observation. Anatomical study of the chambers of the heart has been carried out rather commonly by the injection of opaque masses into the various chambers of the unopened heart in situ in the cadaver, and numerous experiments have been reported involving the introduction of various contrast substances into the blood stream as it enters the heart. Bubbles of air, droplets of iodized oil, and water soluble iodine compounds have from time to time been used. These materials have been introduced through needles placed in large peripheral veins, through catheters inserted through such veins to the entrance of the right auricle, and by way of cannulae passed into the left ventricle through the carotid artery. Because of their hazardous nature such experiments have been conducted for the most part upon animals. Somewhat similar procedures, employing contrast substances which can be administered intravenously with safety, are

used in the study of peripheral vessels. These have quite naturally whetted the appetite of practitioners and experimenters alike for a safe and practicable method of studying the flow of blood through the heart itself. Because of the rapidity of flow and the very rapid dilution to which injected contrast substances are immediately subjected, this problem is not simple in solution. Sizable quantities of very dense fluids are required. It does appear, however, that recent progress in this direction may well result in the development of a useful and feasible means of attacking the problem. Remarkable results in this field have recently been achieved by Robb and Steinberg.

Observations regarding the comparative size of the paired chambers of the heart, the presence or absence of septal defects, the presence and nature of other congenital malformations, the competence of valves, circulation time between various points within the chest, and other features of blood flow through the heart and its great vessels appear to be open for direct study. Perhaps the most promising field of study related to the use of contrast substances within the heart concerns itself with the possibility of identifying beyond question of doubt the vascular or non-vascular nature of obscure mediastinal masses. The frequency with which aneurysms, both pulmonary and aortic, masquerade as neoplasms or inflammatory masses is notorious and any reliable means of direct graphic differentiation will be warmly received.

SUMMARY

Roentgen-rays may be employed in a number of ways in the study of heart disease. The extent to which such methods of study are employed depends in very large degree upon the ability, interest and experience of the observer as well as upon the apparatus and time at his disposal. Such examinations should always include fluoroscopy because intrinsic movements of the heart and changes in its position relative to respiration are so important. However searching roentgen examination may be, the objective findings by it made available are of little value until they have been carefully weighed in the light of other considerations by a competent cardiologist.

DEEP INJECTION OF NOVOCAINE FOR THE RELIEF OF PLEURAL PAIN*

By SIDNEY SCHNUR, M.D., *Houston, Texas*

PAIN is the most important and most frequent symptom in medicine.¹ To the physician it is of value in the diagnosis and localization of disease, but having served this purpose pain should be promptly relieved. When it interferes directly with a vital function such as respiration, relief is urgent. In this latter category is pain of pleural origin.

The treatment of the pleural pain of early pneumonia, pulmonary infarction, etc. has undergone few changes in recent years. In addition to counter-irritants, strapping and sedation with codeine or morphine, pneumothorax has been used recently in the more severe cases unrelieved by the other methods. Morphine has not met with universal favor because of its depressant action upon the respiratory center. Pneumothorax, although relieving pain, is a procedure whose value in pneumonia is still under investigation.

An attempt has been made to relieve severe pleural pain by local injection of novocaine into the pleura. The site of the maximum pain having been indicated by the patient one or more interspaces in this region were infiltrated with 5 to 10 c.c. of 2 per cent novocaine intracutaneously, subcutaneously and into the region of the pleura. Most of the novocaine was injected deeply. An ordinary hypodermic needle for the superficial infiltration and a No. 19 Wassermann type needle for the deep injection were used, care being taken to avoid the intercostal vessels by injecting at the upper border of the rib. Penetration of the parietal pleura may be recognized frequently by an accentuation of pleural pain or suddenly encountering resistance due to consolidated lung. Although it did not appear necessary to infiltrate between the two layers of pleura, piercing the parietal pleura (and presumably entering into the pleural cavity) seemed to give the best results.

Thirty-one cases of pneumococcus pneumonia, and one of pulmonary infarction suffering from severe pleural pain were used as subjects for this therapy. Each of these patients had typical sharp, lancinating pleural pain frequently associated with a grunt and aggravated by cough and inspiration. In most of the cases unsuccessful attempts had been made previously to relieve pain by the usual methods.

Pain. In each of the 31 cases of pneumonia, the sharp pleural pain disappeared immediately. In 25 there was complete relief, while six described a residual soreness. In the former group 18 had no recurrence of pain, while in the remaining seven it returned in five minutes, 10 minutes, 30 minutes, two hours, five hours, 12 hours, and 26 hours. Five of these were

* Received for publication July 9, 1938.

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easily controlled with narcotics or strapping and two were reinjected with partial relief. Of the six patients who complained of soreness after the original injection, three had recurrence of pleural pain in 15 minutes, 50 minutes and two hours. Reinjection aided one, while the other two required morphine for comfort. The case of pulmonary infarction responded immediately to novocaine, but the pain returned in 12 hours after which it could be controlled with codeine. In several patients used as control the pain was unaffected by deep insertion of a needle without injecting novocaine, and in three cases saline injection had little if any effect. In addition to the relief of pain, novocaine seemed to have indirect beneficial results.

Respiration. Each patient prior to the injection exhibited shallow, rapid respiration, the pleural pain obviously preventing full inspiration. Following the relief of pain, respiration was definitely altered; inspiration became deeper, the rate slowed, expiratory grunting ceased, and in several patients there appeared to be immediate improvement in the cyanosis.

Cough. A severe agonizing cough was common. The associated pain frequently prevented the patient from expectorating, thus causing occasional difficulties in typing. After pain was abolished, cough was no longer distressing and sputum could be obtained more easily. In the majority of patients after the injection of novocaine cough was less frequent.

Rest. Many patients studied in this series had not slept for 24 to 72 hours; they were restless and uncomfortable even after the administration of sedatives and hypnotics. The sudden change in some of these individuals after their pleural pain was relieved was striking. Many turned over and fell asleep within 10 minutes after the injection. There also appeared to be a corresponding improvement in the mental attitude.

Prognosis. The factors in the eventual outcome and the incidence of complications in any individual case of pneumonia are varied and numerous, depending on the age of the patient, time of onset of treatment, type of infection, use and amount of serum, alcoholism, etc. Since the cases studied were few and the above factors were uncontrolled, one cannot say at present how injection of novocaine affected the course of the disease. From the clinical point of view, it appeared to be beneficial. Other things being equal, since prognosis is partly dependent upon adequate rest and the relief of all distress and mental anxiety, and these are favorably affected by this therapy, one should expect a more favorable prognosis.

There were no immediate harmful effects from this therapy. Nor was there any apparent difference in the number of cases showing extension to other lobes, pleural effusions, empyemas or pneumothoraces compared to a group of approximately 50 patients in whom this method was not used. Bullowa² in a large series has shown that lung puncture in the diseased area does not carry an increased risk of empyema.

DISCUSSION

The pleural pain of early pneumonia is one of the causative factors in the respiratory disturbance in the disease. The pain, by preventing inspiration, causes shallow breathing. The body response to this is tachypnea. The rapid shallow breathing which obviously causes imperfect alveolar ventilation of normal parts of the lung "is not only uneconomical but may actually increase anoxemia."³ Meakins⁴ states that rapid shallow breathing is one of the principal causes of the anoxemia occurring in pneumonia. Relieving pain which is partly responsible for starting this vicious train of events would seem therefore to be of importance.⁵

The sensory nerve supply of the pleura consists of a plexus arrangement of fibers in the parietal pleura.⁶ These are branches of the intercostal nerves—one small area of pleura usually being supplied by several intercostal nerves. The pleura may be anesthetized by paravertebral, intercostal or pleural block depending on the distance of the nerve from the cord. Weiss⁷ has occasionally obtained temporary relief of pain by intracutaneous infiltration. Paravertebral block is a surgical procedure. Intercostal block is said to be of value when the pleura is inaccessible to direct injection as in diaphragmatic and mediastinal pleurisy. Direct pleural injection is most valuable when small areas are involved as in early pneumonia because all the different fibers arising from a painful area are blocked at the origin necessitating fewer injections, and more important, the anesthesia seemed to last longer.

It is uncertain why a local anesthetic whose action is no longer than two to four hours should frequently abolish pleural pain permanently. In the natural course of pneumonia the pain is of relatively short duration, but it remains longer than four hours in most cases. Therefore the local anesthetic action alone cannot explain the permanent relief of pain. It is possible that the trauma of the injection or the irritating action of novocaine may after a short time cause a small localized effusion which separates the pleura, relieving pain. A localized traumatic pneumothorax due to the injection would probably have the same effect.⁸ In several cases in which roentgen-rays were taken before and after injection, neither fluid nor air could be demonstrated in the pleural cavity. However, at least 150 c.c. must be present before it could be visualized by roentgen-ray, so that this explanation can not be excluded.

SUMMARY

1. Novocaine was injected deeply into the painful area in 32 patients with severe pleural pain and resulted in immediate relief in every one. In 21 of these, pain was permanently abolished. In those individuals in whom pain recurred its severity was much decreased.

2. The beneficial secondary effect of this therapy on other symptoms in pneumonia, i.e. dyspnea, cough, restlessness, and mental state, is described.

I wish to thank Dr. J. Hamilton Crawford, Dr. Carl H. Greene, and Dr. Richard H. Bennett for the use of the cases of their services, in this study.

BIBLIOGRAPHY

1. MEAKINS, J. C.: Practice of medicine, 1936, p. 8, C. V. Mosby Co., St. Louis.
2. BULLOWA, J. G. M.: The management of the pneumonias, 1937, p. 107, Oxford.
3. MEANS, J. H.: Dyspnea, Medicine Monograph, 1924, v, 95.
4. MEAKINS, J. C.: Harmful effects of shallow breathing with special reference to pneumonia, Arch. Int. Med., 1920, xxv, 1.
5. HALDANE, J. S., MEAKINS, J. C., and PRIESTLY, J. G.: The effect of shallow breathing, Jr. Physiol., 1918, lii, 420, 433.
6. GRAHAM, E. A., SINGER, J. J., and BALLON, H. C.: Surgical diseases of the chest, p. 115, Lea and Febiger, Philadelphia, 1935.
7. WEISS, S., and DAVIS, D.: The significance of the afferent impulses from the skin in the mechanism of visceral pain, Am. Jr. Med. Sci., 1928, clxxvi, 517.
8. TCHERTKOFF, J. G.: Rôle of traumatism in induction of initial pneumothorax, Quart. Bull. Sea View Hosp., 1936, i, 398.
9. CAPPS, J. A.: An experimental and clinical study of pain in the pleura, pericardium and peritoneum, 1932, Macmillan Co., New York.

INITIAL MANAGEMENT OF TUBERCULOSIS WITH SPECIAL REFERENCE TO THE PSY- CHOLOGY OF THE PATIENT*

By LEWIS J. MOORMAN, M.D., F.A.C.P., *Oklahoma City, Oklahoma*

THE initial management of pulmonary tuberculosis would be relatively simple were it not for the patient. Modern methods of diagnosis make it possible to observe, record, and evaluate the symptoms and signs of the disease. The nature and extent of anatomic changes may be accurately estimated and, by means of the roentgen-ray, visualized. With all the data available through the application of the usual diagnostic methods, the well informed physician should experience little difficulty in planning the most logical form of management. But, the effective execution of any program based upon symptoms and the purely physical and pathological conditions, must take into consideration the patient's personality, representing, as it does, the summation of all the hereditary and environmental influences of a lifetime.

The physician who thinks he has perfect control of a patient under his initial management, is probably not fully aware of the varied psychological possibilities. He fails to appreciate that herein are often explained some of the differences between animal and human clinical tuberculosis. Personality is constantly affected by the disease, and disease by the personality. If this were not true, the attending physician would be reasonably accurate in his estimate of the problems presented by the three clinical gradations of the disease.

In *minimal pulmonary tuberculosis* the initial management should consist of rest in bed with careful attention to hygienic and dietetic measures, preferably in a sanatorium, but possibly in a well-ordered home.

Moderately advanced. The initial management should be the same as the above, plus artificial pneumothorax or some other chosen form of collapse therapy. However, if all conditions are favorable and the indications for collapse therapy are not clear cut, such measures may be temporarily deferred with the hope of success through routine management. Institutional treatment of such a case is unquestionably preferable to home treatment.

Advanced. Initial management should definitely include sanatorium routine, plus necessary collapse therapy with close observation and careful diagnostic scrutiny for guidance in the probable successive steps of collapse therapy.

The above classification, with suggested management, is deceptively simple, for the constant advances in the diagnosis and management of tuberculosis place increasing responsibilities upon the attending physician. In

* Received for publication April 28, 1938.

doubtful cases he must see that all available diagnostic methods are employed. After the diagnosis is made he cannot well devise a therapeutic program until he has determined whether the case is minimal, moderately advanced, or advanced; whether it is acute or chronic; whether it is predominantly unilateral or bilateral. He must also recognize the presence or absence of cavities, and, if cavities are present, he must determine their size and location, the character of their walls, and the condition of the surrounding tissues. He must determine, if possible, the presence or absence of adhesions and the position and mobility of the diaphragm and the mediastinal structures. He must attempt at least a clinical estimate of the vital capacity of the lungs and he must appraise the cardiovascular system, with particular reference to the integrity of the heart muscle. He must recognize serious complications when present, as well as other associated pathological conditions. These demands require unusual knowledge of the anatomy and physiology of the intrathoracic organs, an appreciation of the pathology of the tubercle from early proliferation to cavity formation, special skill in physical diagnosis, and the wisdom of clinical experience. There must be a choice between home management and institutional management. In those chosen for institutional management, there must be a choice between routine management and surgical collapse. If the latter there must be a choice between artificial pneumothorax, intrapleural and extrapleural pneumolysis, phrenic-nerve interruption and thoracoplasty. Often there must be a decision with reference to simultaneous bilateral or successive bilateral pneumothorax, or a decision regarding cautious combinations of the various surgical procedures mentioned above. Obviously, in many cases, it is unfair to both physician and patient to leave the management of pulmonary tuberculosis wholly in the hands of the family physician. Even among specialists, the successful management of pulmonary tuberculosis demands consultation and team-work.

Thus far, we have briefly outlined initial management in the light of symptomatology and pathology. Unfortunately the disease and the patient are inseparable. Patient and personality are virtually synonymous, and personality finds expression through psychological response to environment.

Often the apparently well-poised patient upon being apprized of the presence of tuberculosis and the necessary therapeutic requirements, may, through the exercise of cultivated inhibitions, artfully conceal mild or moderate psychological conflicts. Nevertheless, these may initiate a physiological imbalance resulting in digestive disturbances, metabolic deficiencies, and a rise in the adrenalin and sugar content of the blood, causing inhibition of phagocytosis and a consequent lowered resistance to the progress of tuberculosis. These changes have been noted through clinical observation and confirmed by animal experimentation. The wise physician may anticipate such an eventuality and employ preventive psychotherapy, or, if he does not immediately sense the psychological difficulties and the patient is not exhibiting satisfactory response to management, he may be able successfully to

penetrate the veil of graceful acquiescence and discover existing occult psychological conflicts.

More emotional and less stable persons, upon being informed of the presence of tuberculosis, may immediately burst into tears and, if dramatically inclined, may fill the air with lamentations. In their misery, they often have genuinely sympathetic family confederates ready to magnify these psychological conflicts with uncompromising pertinacity. In many cases, this distressing complex may be promptly, or at least gradually, modified through education, which may replace exaggerated ideas with consoling facts artfully presented by a sympathetic, far-sighted physician.

Occasionally we find patients stricken with even more serious psychological conflicts, seeking the protection of silence. These individuals are in dire need of psychiatric help or even of psychoanalysis, and prompt measures should be directed toward a better understanding on their part of their physical condition, its therapeutic implications and probable prognostic possibilities. Well planned persistent efforts on the part of the attending physician with oft repeated conferences, may succeed in making a good soldier of a psychological weakling or a whimpering coward. Because of innate instability of the nervous system in certain cases, the obstacles may be insurmountable and the end hastened by continued anxiety and the consequent lowered resistance. Rarely in desperation, suicidal impulses may arise and surcease may be sought through self-destruction.

The patient's domestic and social situation is very important. For parents, the mental strain either of being in contact with their children or of leaving them behind is always a factor influenced favorably or unfavorably by the age, character, and temperament of the children, and by the environmental conditions, such as the adequacy and safety of home care, including all of the accustomed domestic amenities. Adoring mothers who cherish an abiding sense of sacrificial duty well performed, cannot surrender their position without psychological conflicts which may, in some cases, prove a serious handicap. Such difficulties may be overcome by convincing the mother that contact with children should be broken and management faithfully accepted in order that she may later safely resume her place in the home.

Separation of husband and wife, particularly in cases requiring sanatorium care, may occasionally lead to insurmountable psychological conflicts. Here the range and scope of evil possibilities hinge upon the character and temperament of the respective personalities and their ability to maintain equable social and moral standards under abnormal conditions. There is nothing so discouraging as domestic infelicity, especially when accompanied by the haunting fear of inconstancy. Not infrequently, an irresponsible personality with unstable psychological susceptibilities, may manifest serious conflicts because of wholly unwarranted fears. Such evil fears spring from a vivid imagination impregnated with the groundless illusions which so often follow physical inactivity. On the other hand, the attending physician occasionally finds an unsuspecting soul while "singing at her grinding,"

suddenly shocked by the deadening consciousness of a faithless spouse. Nothing leaves one so inert, so devoid of psychological response, so unfit for disciplined battle.

Unmarried lovers may suffer similar conflicts, often magnified by the fear that chronic invalidism may cool the ardor of a coveted suitor. Such fears may lead to the precipitate negotiation of matrimony with all the hazards of such an untimely union.

These problems of the heart place upon the attending physician varied responsibilities. Some may be successfully executed through the exercise of ordinary skill, while others may require more than the wisdom of Solomon. However, with openness of mind, the physician learns in the school of life daily lessons, and develops a certain skill in giving more than is demanded by strict measure. Through such giving, tolerance is broadened, perception is sharpened, and initiative finds its course. The exigencies of each case must suggest the method, which will necessarily depend upon the character of the metal, the heat of the forge, the weight of the hammer, and the desired result.

The resourceful physician, with sincerity of purpose and straightforwardness of action, may succeed in bridging gaping chasms and in healing sensitive wounds. As may be said of physical scars, psychological scars often memorialize heroic deeds. Such memorials should rest securely among the unheralded satisfactions of a doctor's life.

Obviously the wide range of psychological manifestations makes adequate discussion impossible. The attending physician must be ready to meet the needs of his tuberculous patients as they come from every stratum of society, psychologically geared to keep pace with this fast-going, highly scientific, mechanistic age in which mankind has seemingly turned from reliance upon religion toward the more tangible, yet in the end, less satisfying guidance of science and reason. When faced, however, with what they consider a serious life hazard, patients almost without exception, seem to suffer from an obvious sense of personal insufficiency and a need for an abiding faith in some unseen power or outside agency. Ibsen had this in mind when one of his characters, under emotional strain, is represented as saying: "Without a fixed point outside myself, I cannot exist!"

Even anti-Christian, self-sufficient Goethe, when threatened with destruction by storm on the rocks of Capri, quieted his terrified fellow passengers by urging them to pray and by reminding them of Christ walking on the water. The dangerous agitation of panic-stricken passengers brought prompt realization of their need of some anchor outside themselves. Though Goethe was then approaching forty years of age, his own mind swiftly reverted to childhood teachings for this stabilizing influence. After his priestly task was performed, he admitted "a certain sense of pleasure which seemed to derive from the Lake of Tiberias, for I could quite plainly see the picture from Marian's illustrated Bible hovering before my eyes."

Henry C. Link's book, "The Return to Religion," was inspired by a

recent exhaustive study of current psychology as influenced by the long financial depression. He feels that a return to religion offers the best solution and that the Bible remains one of the most promising texts for the solution of fundamental psychological conflicts. However, there are many avenues of approach and innumerable sources of help for the patient who is groping in the dark. A broad knowledge of literature, history, and biography will better enable the physician to interpret his patient's psychological needs and without being suspected of a designing interest to direct his reading along therapeutic lines. Often the most essential and helpful initial educational adventure is teaching the patient the plain truth about tuberculosis. The story in language he can understand is often a source of great comfort and seldom is it wholly discouraging. Rarely is a patient's condition so serious as to preclude the possibility of a ray of hope, based upon the application of acquired knowledge in the diagnosis and management of his own case. However, in many patients the truth should be given in graduated doses, never exceeding psychological tolerance.

The more nervous and fearful the patient, the more important the sanatorium becomes in the initial management. The daily contact with physicians, nurses, and other patients in a well ordered sanatorium life usually serves as a revelation, inspires confidence, increases knowledge, and dissipates fear, thereby creating the best possible conditions for progressive improvement. For many there is nothing more hopeless than to lie down at home with the shocking consciousness of the intimate presence of a dread disease, fully aware of the partially concealed anxiety of poorly informed yet sympathetic loved ones, obviously ignorant of the patient's most urgent needs. Genuine poverty and the necessary household penury often serve as aggravating factors. Such an environment encourages dangerous introversion and may cause the patient silently to hug his own burden of bitterness through long days and nights, tortured with a hopeless sense of fear and uncertainty and possibly harboring the spirit of rebellion so common in the course of a great catastrophe.

The attending physician must ever keep in mind the fact that mental adaptability is limited by individual characteristics and that psychological adjustments, though difficult, must be made a part of every initial therapeutic program in order that valuable time may not be lost. It is difficult to pursue an effective educational program in the home, yet it is not impossible. Through the patient application of the attending physician or the well-trained public health nurse, the acquisition of knowledge and understanding may replace doubt, fear and rebellion, with hope and its attendant virtues.

The psychological appraisal of the patient and the educational program should have their inception when the patient first enters the physician's presence. The latter's success will depend upon his own knowledge of human nature and what Oliver Wendell Holmes called "intuitive sagacity." From the moment of first contact with the patient, the wise physician will be gathering information which will serve as a guide in making plans for his

initial management. By the time his diagnostic studies have been completed he will have, at least partially, determined the psychological trends and his conclusions will materially aid in the choice between home and sanatorium management and the determination of educational requirements.

The education of the patient is definitely a part of the physician's responsibility and should be wholly in his hands or under his direction. It is well to remember there is no short cut, no swift approach, no possibility of sudden arrival. It requires infinite patience, well-poised perseverance, adequate resources, and genuine spontaneity, with generous lessons which never exceed well guarded reserves. It should be designed to meet each patient's needs and should support the attending physician's method of management. As a part of initial management, this becomes invaluable to both physician and patient. If education is not properly supervised, the patient may discover conflicting opinions as to practices and procedures and may be tempted to depart from his physician's instructions. This disturbs confidence, interrupts therapeutic routine, and may create unfavorable psychological conflicts.

Physicians, nurses, and social service workers must constantly guard against thoughtless remarks which may be misconstrued. A misplaced word may prove serious. A passing remark by a friend or another patient may result in a wakeful night or a week of useless anxiety. The educational program and the daily routine should be designed to prevent or to meet such psychological events. The physician on regular rounds immediately observes obvious conflicts and if the need arises makes an effort to discover concealed fears and worries.

It is not uncommon to find the patient secretly worried about new symptoms or signs, or the aggravation of old ones. It may be shown that such worries are unwarranted or even when justified by pathological changes, the mental conflict may be corrected by a careful explanation, especially if there is a reasonable hope of prompt improvement. Otherwise, such conflicts may go on indefinitely. John Keats was driven to Italy by a streak of blood; Shelley was similarly impelled by persistent symptoms and signs; Robert Louis Stevenson finally staked his last dollar on a seventy ton schooner because of unabated toxemia, and unresolved psychological conflicts.

Early in the course of treatment the patient should be impressed with the fact that both mind and body must be wholly committed to the task of getting well and that there is no respite. Through proper education, he must be directed into avenues of self-expression and the execution of enlightened responsibility. Finally, every patient must learn with Carlyle that the duty of being brave is an everlasting duty, even though it may lead to the last great mystery.

This discussion of psychology must not end without calling attention to the fact that the success of initial management may depend largely upon the patient's estimate of the attending physician. We must not forget that while we are examining patients, patients are examining us. Of all the

patients who have spoken, none is more worthy of a hearing than Henri Frederic Amiel:

“Why do doctors so often make mistakes? Because they are not sufficiently individual in their diagnoses or their treatment. They class a sick man under some given department of their nosology, whereas every invalid is really a special case, a unique example. How is it possible that so coarse a method of sifting should produce judicious therapeutics? Every illness is a factor simple or complex, which is multiplied by a second factor, invariably complex . . . the individual, that is to say, who is suffering from it, so that the result is a special problem, demanding a special solution, the more so the greater the remoteness of the patient from childhood or from country life.”

“The principal grievance which I have against the doctors is that they neglect the real problem, which is to seize the unity of the individual who claims their care. Their methods of investigation are far too elementary; a doctor who does not read you to the bottom is ignorant of essentials. To me the ideal doctor would be a man endowed with profound knowledge of life and of the soul, intuitively divining any suffering or disorder of whatever kind, and restoring peace by his mere presence. Such a doctor is possible, but the greater number of them lack the higher and inner life, they know nothing of the transcendent laboratories of nature; they seem to me superficial, profane, strangers to divine things, destitute of intuition and sympathy.”

THE LIMITATIONS OF GOVERNMENT IN MEDICINE; THE SAN FRANCISCO EXPERIENCE*

By J. C. GEIGER, M.D., F.A.C.P.; A. E. LARSEN, M.D., and J. P. GRAY, M.D., *San Francisco, California*

INTRODUCTION

RECENT months, more than ever before, have seen the development of concentrated interest in and extensive discussion of the problems of medical care, particularly as to governmental participation in their solution. The mere fact that representatives of the various groups interested in the problem, from all sections of the country, have met in important conferences of national scope to discuss all aspects (medical, economic, sociologic and administrative) in itself demonstrates progress.

American medicine today leads the world—scientifically and in all its humane aspects. Much of the discussion is built around public health and the lack of medical care. Public health, as such, is really not the duty of organized medicine. It is the duty of government, whether it be city, state, or national. Therefore, if there has been any neglect of public health in any locality, the blame should be placed where it belongs—on government. Certainly in San Francisco organized medicine has always supported the Department of Public Health. The politician (at least in the past) has not seen the vote-obtaining possibilities in humanitarian activities of government, such as public health. The fact remains that many of these activities originate from physicians, nurses and medical social workers and not from the government, though the latter is usually quick to absorb them. There must be realized, too, the critical and often adverse reaction of tax payers to accelerated budgets for such activities.

Adequate medical care in all its ramifications (which would include clinics, dispensaries, hospitals, and the necessary laboratory tests and home visits) should be divided into three groups: (1) those who cannot pay because of a disproportion between income and their medical needs; (2) those who should pay but find themselves in great difficulty because of their own budget limitations and ineptness in planning for illness; and (3) the smaller group who can pay for anything at any time.

Experience with the first group is available in San Francisco. With the second group, there is no doubt that medical opinion has been divided, but that division is more apparent than real. The division is in two schools: (1) compulsory health insurance, which many feel very definitely that these United States should never adopt in spite of the many good and acceptable features in several European countries; (2) voluntary health insurance

*Read at the New Orleans meeting of the American College of Physicians March 27, 1939.

which a large portion of the medical profession thinks should be the American system and whereby the patient may have, at a reasonable cost (not yet absolutely determined), choice of hospital and choice of physician. The dentist and the nurse, especially in home care visits, are seldom, if ever at all, mentioned in such a scheme, and yet the nurse is indispensable for the care of the ill, as is likewise the dentist in a great variety of diseases. Moreover, the seeming neglect of postgraduate training for the physician is an oft-repeated challenge not yet entirely answered by organized medicine or the medical colleges.

In the San Francisco set-up the limitations of government in medicine are thought consistent and there is no medical or public health neglect within the budget allowed. Moreover, the Department of Health lives in peaceful existence with organized medicine. If the program of public health should include hospitalization and home care of the indigent (classified as such because of their medical needs and limited earning capacity), which has not been the case heretofore, then again the matter is for government through health departments, and not through organized medicine. It is the rule rather than the exception that physicians give of their time, skill, and energy, without compensation. Even if this problem could be solved and properly budgeted to include the physicians, there still would remain the care of the moderate income group. It is this group that becomes the *pièce de résistance* for argumentative health insurance advocates.

For the reason that the experience in San Francisco has been rather widely recognized as having certain unusual aspects, it is believed appropriate that these be described in some detail so that the experience in this one metropolitan area may be available to others, not because the San Francisco experience is in any sense set forth as the ideal, but rather that attention may be invited to the limitations of the system as well as to the progress that has been made in this one community over a period of years.

San Francisco, a cosmopolitan population group of approximately 690,000, occupies an area of less than 50 square miles of hilly terrain at the tip of a peninsula, surrounded on three sides by waters of the Pacific Ocean and San Francisco Bay. With the facilities of one of the world's finest harbors available on its waterfront, San Francisco has developed into one of the largest American ports, and has been referred to, aptly, as the gateway to the Pacific. The metropolis is recognized as the commercial, transportation, and financial center of the Pacific Coast. Of interest also, in the presentation of the subject of this paper, is the fact that the community has a city and county form of government under a freeholders' charter, with noteworthy stability of administration.

From the medical point of view, San Francisco has many advantages as well. It is the medical center of the Pacific Coast, being the seat of two outstanding medical schools (the University of California and the Leland Stanford Junior University); three great hospitals operated by the Federal Government (the Letterman General Hospital of the United States Army, the

Marine Hospital of the United States Public Health Service, and the Diagnostic Facility of the United States Veterans' Administration); the nationally recognized San Francisco Department of Public Health, which includes the San Francisco Hospital; extensive hospital and outpatient services in non-official or voluntary hospitals of high standard, and, for the dependent portion of the population, a medical care program providing both inpatient and outpatient services that has attracted the attention and favorable impression of prominent students of public welfare and public health.

The integration of these various facilities into the whole community plan is not complete, but progress toward this objective, it is believed, merits description.

THE OFFICIAL SERVICES

Official agencies in the medical care program in San Francisco are two departments in local government (the City and County of San Francisco), the Department of Public Health and the Public Welfare Department, and one branch of the State government, the State Relief Administration in San Francisco.

THE DEPARTMENT OF PUBLIC HEALTH

Among health departments of major cities of the United States, the San Francisco organization has the same unique status of including the institutions maintained by the municipality for the care of the indigent sick, infirm and aged. Of no little import in the maintenance of balance between preventive or orthodox public health services and curative or institutional services, is the fact that the direction of the Department has been and is placed in the hands of a public health administrator rather than a hospital administrator.

The Department is set up in three sections, all of which participate in the program: the technical section (non-institutional and non-medical services, including vital statistics, laboratories and the inspectional bureaus; the medical-dental-nursing section (non-institutional medical services, as communicable disease control, child health services, public health nursing); and the institutional section (the San Francisco Hospital, the Laguna Honda Home, the Hassler Health Home and the Emergency Hospital Service). More closely allied to the institutional section administratively, but also very closely related to the medical-dental-nursing section, are the chest diagnostic centers, the outpatient obstetrical service, the venereal disease diagnostic and treatment centers and the city physicians, treating persons in their homes.

The technical section activities, although non-institutional and non-medical, provide services of importance to the public health of San Francisco, particularly in food and milk control, laboratory service, industrial hygiene and plumbing inspection. But of more specific interest to the subject of this paper are two other services: vital statistics and housing inspection.

Vital statistics, in the San Francisco Department of Public Health, has been extended beyond the study of mortality, natality and morbidity, in the ordinary sense, to include the study of statistical data from all sections of the department, including other technical services and the institutional services. This richest source of information serves the Director of Public Health, the Department, and the community in presenting data pertinent to the problems of public health and medical care.

Housing, as a factor in public health and public welfare, is recognized today as highly important. Although the extent of the sub-standard housing problem in San Francisco is perhaps not as great as it is in many of the older centers of population in the eastern part of the country, the problem does exist to considerable degree. For more than 20 years the State Housing Act has been an effective legislative instrument permitting improvement in housing in San Francisco and other cities of California. The Housing Inspection Division of the Department of Public Health has been responsible for the abatement of many nuisances, the demolition of large numbers of unsafe, unsanitary and unhygienic buildings used for dwelling places, with the result that the under-privileged persons living in such surroundings and under such conditions have had to live in other quarters which were at least less hazardous to health and happiness.

Partly, as a result of this type of work, there has been organized by ordinance the San Francisco Housing Authority which, through Federal subsidy, has been allocated funds of at least \$15,000,000. If a health department decides in its wisdom to destroy tenements that are unfit for human dwellings, then it is equally logical to demand dwellings for replacement. It remains to be seen how effective the efforts of the San Francisco Housing Authority will be in supplying suitable buildings for this low income group.

The services within the medical-dental-nursing section, obviously, are directly related to the preservation of the public health. In the Bureau of Child Hygiene, all child health services are brought together in the administration of district health centers, well-baby conferences, school medical and nursing services, dental services, prenatal and postnatal supervision, nutritional work and the care of physically handicapped children. Public Health nursing, administered as a division within the Bureau of Child Hygiene, permeates the entire field of child health and, indeed, it is in this group of activities particularly that there is demonstration of the truth of the dictum, "the public health nurse is the wheel-horse of the public health organization."

As in several other cities, the district health plan takes the services of the health department to the neighborhood. The well-baby center is open to all children, without respect to socio-economic status, as an educational function. No treatment is provided for the sick child; in such instances referral is made to the family's physician or to a clinic if the family is unable to pay a physician. Dental care, for children up through the tenth year, is provided for those whose parents cannot afford the services of a

privately practicing dentist, the care consisting of prophylaxis, extractions and fillings. No orthodontia or prosthetic work is attempted in the service, since the facilities and personnel do not permit the long term, highly specialized and individualized care that such a program would require. A minimum amount of funds is available, however, for this type of dental care, but the needs far exceed this amount.

School medical and nursing services include medical inspection of school children, with special diagnostic problems studied in a well-equipped diagnostic center (electrocardiography, roentgenology, fluoroscopy, ophthalmoscopy, etc.), including audiometer testing and close working relationships with sight conservation classes, health schools and similar special facilities. There are in all two health schools, seven health classes, five sight saving classes, one school for the deaf, two contact classes for the hard of hearing, and the Sunshine School for crippled children.

All medical and nursing services in the public schools, parochial schools and junior college are coördinated under the Director of the Bureau of Child Hygiene within the Department of Public Health. The medical examination of school children by the family's own medical attendant is encouraged, and, under an arrangement worked out between the Department and the San Francisco County Medical Society, these examinations are reported by the physician to the Health Department on forms supplied and distributed through the Schools. Immunization against diphtheria and smallpox are not offered in the schools until three months after the physician has been requested to do so in connection with his examination of the child. The correction of remediable defects has been encouraged as a function of the physician, too, rather than of the public service, if the parents can provide the care. The supplying of glasses is through public funds which are totally inadequate. The success of the plan, which has been in effect in San Francisco over a period of three decades or more, lies in the interrelation between the Department of Education and the Department of Public Health. The Director of the child health services serves as the liaison officer between the Director of Public Health and the Superintendent of Schools, so that there is every opportunity for clearance of problems through an established channel.

Prenatal and postnatal instruction and guidance are provided by public health nurses and physicians working with patients registered in the outpatient obstetrical service. Group instruction is given in the center, and individual instruction in the home. The service is available to any pregnant woman having legal residence in San Francisco, if she is unable to provide medical care for herself, or if her physician requests such instruction. The patient is seen by the physicians of the outpatient obstetrical service at regular intervals during pregnancy, and concurrently the nurses make home visits. With the onset of labor, multiparous women are cared for at home if conditions therein are suitable and no complications of labor are manifest; and primiparous women are taken into the San Francisco

Hospital's obstetrical service. After the post-partum period, the public health nurse continues to guide the mother through return visits to the outpatient obstetrical center for follow-up of the mother's condition and visits to the well-baby center for diet supervision and habit-training for the baby. For the very low maternal and infant mortality rates in the group served by these two services, even lower than the notably low rates that obtain for the city as a whole, San Francisco can well be proud.

Nutritional work, particularly with children of school age, has been done only to a limited extent. Dental hygienists in the dental unit of the child health services carry out a rather intensive health education program, working with a supervisory public health nurse. Studies have been made by physicians and nurses in the Bureau of the nutritional status of children in the schools, with comparisons drawn between those not receiving relief and those receiving relief, in the days when "relief in kind" was given. Perhaps at this time the fact is worthy of note that this study showed that a better state of nutrition was found in the group from families receiving relief than that found in the "control" group, that is, from families not receiving relief. For the underprivileged school children milk is furnished in the school cafeteria at public expense, those receiving milk being selected by the principal of the school. Complete hot meals are provided those handicapped children attending the two special health schools.

For over 20 years California has had a state law providing care for crippled children. Since in San Francisco the official public health agency has all the facilities for the care of such handicapped children, the entire problem, from special care in schools to highly specialized orthopedic care in the San Francisco Hospital, is coördinated in the child health services. Finally, children who are wards of the Juvenile Court are supervised medically by physicians from the Department of Public Health, each child receiving a complete physical examination and having appropriate care and treatment outlined and arranged for him.

Facilities for the diagnosis and treatment of venereal disease, heretofore handled on a coöperative basis with the Outpatient Departments of the two University Hospitals, were recently developed more fully as a function of the Department of Public Health with the support of the State Department of Public Health. With aid from federal sources (United States Health Service under the Social Security Act) through the State Department of Public Health, additional clinic facilities have been secured and the epidemiologic aspects of syphilis and gonococcus infection likewise are being developed to a level comparable with the epidemiologic studies made of the other communicable diseases.

Chest diagnostic centers are maintained by the Department in conjunction with the outpatient clinics of the two University Hospitals, in one voluntary hospital and the San Francisco Hospital. Any physician may refer his patients to these centers for study, examination, tuberculin testing and roentgenologic investigation. Adolescent school children are given

tuberculin tests and roentgen-ray follow-up of all reactors is arranged through the school diagnostic center, all within the child health services. If hospital care is indicated, the chest diagnostic centers and the school diagnostic center feed into the San Francisco Hospital through the social service of that institution.

The institutional services of the Department include: the San Francisco Hospital, a general hospital of about 650 beds, 500 beds for the care of the tuberculous, 120 beds for the care of those affected by other communicable diseases; separate maternity and psychopathic units of 130 and 88 beds respectively; the Laguna Honda Home of 2,000 beds, which is the relief home for the aged and infirm who need institutional and custodial care; the Hassler Health Home of 110 beds for the care of tuberculous of good prognosis; and the Emergency Hospital Service comprising six stations and ambulance service for emergency first-aid treatment at all hours.

A recent bond issue of \$1,600,000, supplemented by P. W. A. funds of \$1,000,000, will allow the Department of Public Health to expand its hospital facilities to include the modernization of the San Francisco Hospital, additional facilities at the Hassler Health Home for the chronic tuberculous, and, perhaps, the convalescent, and an additional medical hospital building for the Laguna Honda Home for the care of the chronic patients.

The San Francisco Hospital, giving inpatient care to approximately 13,500 patients yearly, is used as a teaching hospital by both the University of California Medical School and the Stanford University School of Medicine. The scope of the work done, as well as the quality of the service rendered the indigent sick of San Francisco, is unsurpassed on the Pacific Coast. Testimony to the attitude of the community toward the institution which it maintains for its indigent sick is found in the fact that budgetary needs have been met with consistency by increases from year to year, even through these last several years of stress. The advantages to the two medical schools have been great, obviously, but the City and County of San Francisco have been the recipients of service from some of the greatest medical minds of the West as regularly visiting members of the staff. This hospital is guided by an executive staff selected from the faculties of the medical schools of the universities, and members having the rank of professor. The remainder come from the staff of the Department of Public Health. There are included special committees on therapeutics, pneumonia, acute anterior poliomyelitis, laboratory practices and emergency hospital procedures.

Admissions to the San Francisco Hospital and other institutions of the Department are handled through the social service department. Of more than 27,000 applicants yearly, approximately half are found eligible on the basis of standards of residence, indigency and need for hospitalization. The San Francisco Hospital is maintained for those residents of San Francisco who are in need of hospital care and unable to provide it for them-

selves. The person able to pay his physician and a hospital, on a full or part-pay basis, is not accepted for care.

There is no part-pay plan in effect. If a patient is admitted in an emergency under circumstances precluding investigation, he is removed to another hospital as soon as his condition permits and he is billed for his treatment at rates set annually by the Board of Supervisors. For obvious reasons, the standards for admission are somewhat less rigid for tuberculous persons, for others whose illnesses are of similar chronic type requiring long-term care and for those affected by acute communicable diseases for which facilities are not available in other hospitals. Standards of eligibility are maintained by the social service, with certain flexibilities as indicated above left to the discretion of the Director of Public Health, but it is to be emphasized that the institutions of the Department are maintained for the indigent and medically indigent, and under no circumstances is the hospital in competition with privately operated, endowed, or other non-official institutions.

It is believed appropriate at this point to emphasize the fact that, while certain limited outpatient services are provided in some of the units already presented (outpatient obstetrical service, chest diagnostic centers and venereal disease diagnostic center, and, in a remote sense perhaps in the well-baby centers, school diagnostic center and dental centers), the City and County of San Francisco does not maintain a true outpatient clinic. To facilitate the subsequent observation of persons treated in the hospital, there is maintained a follow-up clinic, to which persons discharged from the hospital return for study and observation over longer or shorter periods. The Emergency Hospital Service does not provide care on a revisiting basis, referring patients treated therein to their own physicians or to clinics. For many years the general attitude of all concerned has been that the interests of the community might be served best if the outpatient clinics and dispensaries maintained by and in connection with the universities and various voluntary or non-official hospitals supported in part by the Community Chest of San Francisco were utilized to the fullest extent. The establishment of an outpatient clinic as a part of the San Francisco Hospital, properly equipped and staffed, would involve great capital investment and high annual budget expenditure, much of which has been avoided by a fuller utilization of already existing facilities.

The Laguna Honda Home, formerly known as the Relief Home, provides institutional care for the chronic aged and infirm. The present plant, constructed during the past twelve years and one of the finest of its kind in existence (and to which will be added a new building), has a capacity of 2000 beds. From an institution giving custodial and ambulatory care primarily, with an infirmary providing hospital-type care for a small proportion of the Home's population group, there has developed the reverse condition during recent years. The institution is rapidly becoming one in which the hospital care for those affected by chronic diseases is of primary import

and the custodial type of care is less dominant. Recently, with the development of the pension program, many aged persons leave the Home to receive an old age pension and live outside the institution, with the result that frequently they require hospitalization on readmission to the Home. As in the case of the San Francisco Hospital, the visiting staff of the Home is made up of members of the faculties of the two medical schools, and the Home is one of the teaching institutions utilized in the curricula of the two schools. Admissions are arranged through the social service of the San Francisco Hospital.

The Hassler Health Home at present is a small (110 bed) institution, located in the hills of the peninsula about forty miles south of San Francisco, maintained for the care of the tuberculous of good prognosis. The persons cared for in the Home are of the younger age group and usually stay for periods of from six to 12 months. Selection is made in the wards of the tuberculosis division of the San Francisco Hospital, from which source all patients in the Home come.

The Emergency Hospital Service, in many cities more closely identified with the Police Department, is a unit within the Department of Public Health. Five units strategically placed operate on a full 24 hour basis and a sixth on week-end and holiday schedule, providing a radio-controlled ambulance service and first aid treatment by physicians assisted by nurses and stewards. No restrictions as to socio-economic status are applied to persons requiring emergency care, but the emergency hospitals are limited in scope of work to emergencies. If more than first aid is required, the patient's physician and the hospital of his choice are informed of the facts. If the patient has no physician or hospital choice, referral is made in rotation through lists of county medical society members and approved hospitals. Those who have no means of providing their own physician or hospital care are referred to the San Francisco Hospital and are admitted, except in emergencies, through the social service. The Emergency Hospital Service, medically staffed by young, well-trained physicians who have had good hospital background and rotate through the service on a two-year appointment usually, serves more than 65,000 persons annually.

Augmenting the San Francisco Hospital and the Emergency Hospital Service in providing a medical service in the home is the group of city physicians. These men, on part-time, long-term appointment, are available throughout the day and evening hours for any person who needs a physician in the home, but not necessarily hospital or even emergency hospital care. The city physician determines the need for hospital care or further home care, and no one is denied his request for one call, although repeat calls are not made if it is apparent that the person can afford his own medical attendant. Prescriptions written by the city physician are filled without cost in the pharmacy of the San Francisco Hospital.

So much for the Department of Public Health.

THE PUBLIC WELFARE DEPARTMENT

The Public Welfare Department was created by charter amendment in 1937, and, in its present set-up, combines the general relief program for the arbitrarily defined "unemployable unemployed" with the public assistance program for the needy aged, needy blind and dependent children. General relief to the unemployed, constituting the "employable" group, is administered in California as a state program, hence the breakdown into the artificial and arbitrary categories of "employable" and "unemployable" persons.

In the Public Assistance Division of the Public Welfare Department, more than 9,000 aged persons receive old age assistance, 450 blind receive blind aid, and 575 families including 1450 half-orphan children receive aid to dependent children, all outside institutions. The grants-in-aid for those under-privileged persons are made up of moneys from federal, state and local funds, under the federal social security act and the California welfare and institutions code. An additional group of dependent children receives aid from these same sources through the Juvenile Court, the division of administration of the program dating from 1913, 25 years ago.

In the Relief Division of the Department, approximately 3,400 cases representing about 5,700 persons, all found to be unable to carry employment, receive relief in the form of a check at semi-monthly intervals, and milk delivered daily to the home. A close working relation exists with the State Relief Administration in San Francisco, in that a common intake service obtains; each organization has its own district staff in the same district office; a common intercity service maintained by the Department serves both agencies in answering inquiries from other governmental units; and, of greater interest medically, the Central Medical Bureau serves recipients of relief from both agencies.

CENTRAL MEDICAL BUREAU

San Francisco, like other metropolitan areas throughout the nation, has in recent years been faced with the problem of providing medical care for the increasing number of persons receiving public assistance. This problem was recognized as far back as 1932. A committee was created to study the situation and to make recommendations to meet the need. This committee was composed of representative persons and included the deans of both local universities, the Director of Public Health, the president of the County Medical Society (who at that time was the Director of Public Health), other physicians who had served terms as presidents of state or local societies, a representative of labor, and one from the woman's clubs. The chairman was a layman who had had long experience as a member of the Board of Public Health. The recommendations of this committee resulted in the formation of the Central Medical Bureau.

The basic theory of operations for this bureau was to act as a central

medical intake for all cases receiving public assistance. It was to divide the medical case load into simple and complicated cases, treating the more simple at the bureau and referring the more complicated to existing clinic facilities throughout the city. In essence it was to be a "buffer" clinic and was intended to reduce the patient load in the already crowded outpatient system.

In addition the Bureau was to coördinate all existing public medical services in home, ambulatory and hospital care.

On this basis the Medical Bureau has been successfully operated for the past seven years. It has survived the changes of several administrations and has been financed at various times by the county, state and federal governments. In 1934 it received approval of the United States Public Health Service, which at that time was administering medical funds, to proceed as an experiment in medical relief. It was then taken over by the State Relief Administration.

The same medical director who developed the Bureau was kept in charge through these changes. He was originally selected upon the recommendation of the advisory committee. This committee has also been active throughout the existence of the Bureau, has acted in matters involving community policies, and has left the Bureau to do a medical job without evidence at any time of political interference. The quality of medical service produced has been excellent.

No attempt is made here to go into the details of operations of the clinic, as this is to be published in the near future in *Modern Hospital*. It would be well here to emphasize some of the outstanding facts about this Bureau which have made it unique in its field.

It offers a medical service to the entire case load with a minimum of delay. People receiving public assistance are eligible to receive care on the presentation of a card of identification, which is checked against a master file. This step requires only a few seconds.

From a professional point of view, all diagnostic work indicated can be performed; there is continuity of treatment from the home through the clinics to the hospital, and proper follow-up after discharge from the hospital.

There is a staff of 50 physicians who are paid salaries for part-time work. These are selected from the recent graduates of approved medical schools. They work an average of nine hours per week. This allows the younger physician to become established in the community and prevents clinic staleness. An important feature of the medical staff is the ability to expand and contract according to the case load. This feature prevents overloading with its possible consequences of reduced quality of medical care.

The Bureau has accumulated over 70,000 medical charts. They differ from the usual chart in that all home care, clinic and hospital information is included in the one chart. In addition, there may be social histories and a statement of medical-social problems. This is a necessity, for the social

treatment of an illness is often required to complete the physician's recommendations.

A close tie-in of the medical service has been effected by means of reports and conferences. In this way the one center is available for county, state and federal problems. The advantages of this can be readily seen as a saving to the taxpayer and a coördinated service when physical factors are concerned.

Because the Bureau serves an entire case load for all types of illnesses, the medical problems of the relief group are accurately exposed. Figures for several years reveal an incidence of illness approaching 20 per cent.

Costs are also accurately known. The complete service, which includes home and ambulatory medical care, dentistry, appliances, visiting nursing service, drugs, physicians' services, nurses, technicians, clerical help and overhead, costs in round figures about \$18,000 per month. This amount is spent in the care of about 25,000 persons. The cost per person then for all services except hospitalization is approximately \$9.00 per year. Hospital care is not included in this figure, being provided by the San Francisco Department of Public Health in the San Francisco Hospital.

While the Central Medical Bureau has received national recognition as an efficient system providing a good quality of medical care at a reasonable cost, there remain many possibilities for other developments. These would include expansion in the fields of rehabilitation by means of elective surgery, the development of a larger psychopathic unit to meet a special problem known to exist in the relief group, the consideration of providing intermediary type of hospitalization where indicated for subacute and chronic conditions, and home care for the aged.

There are also many opportunities for medical research with the group. The development of medical records which are cross-indexed with an available social history provides an abundance of material which may be used in various ways. It provides the opportunity not possible heretofore in metropolitan areas of following and studying a fixed and known section of the population.

Non-official services of considerable importance in the successful experience in San Francisco include the San Francisco County Medical Society, the Community Chest of San Francisco, the schools of medicine of the two universities, hospitals and outpatient clinics, and various voluntary hospitals and outpatient clinics.

The San Francisco County Medical Society has been alert to the community needs and problems to the extent of active interest and participation in community action to meet those needs. The society has been represented on the Health Council of the Community Chest, the Health Advisory Board of the Department of Public Health, and on the Central Medical Bureau Advisory Committee. The society's own committee on clinics and dispensaries has been of no little import to the Community Chest and the Department of Public Health in securing uniform practices and high stand-

ards in these institutions. The Director of Public Health, who served as the president of the society in the recent past and on the Medical Advisory Board of the Central Medical Bureau, Community Chest, etc., has given the Society many opportunities to participate in the planning of the department and members of the Society opportunities to serve on his consultant staff, paralleling the advisory committee on the Central Medical Bureau to the Public Welfare Commission and the State Relief Administration.

The Community Chest has had a rôle to play in the San Francisco experience in the relationship of its Health Council, made up of representatives of voluntary health agencies supported in part by the Chest, and its Hospital Council, made up of representatives of those hospitals receiving Chest support. The discussion of mutual problems with recognition of both community needs and limitations of official agencies, has fostered team work between official and non-official health and welfare agencies. Outpatient clinics of various hospitals have been able, through the councils, to arrive at interrelationships of importance in the whole plan, yet at the same time to preserve their own identity and autonomy in many respects.

As emphasized earlier, the members of the visiting staff of the San Francisco Hospital are members of the faculties of the University of California Medical School and the Stanford University School of Medicine. Over a period of many years, the working relations between the medical schools and the Department of Public Health have been close and of mutual value. During more recent years, there has developed a similar interrelation with the State Relief Administration and the Public Welfare Department. In any plan for a program of medical care at public expense, the teaching institutions must play important rôles. Large outpatient clinics maintained by the two universities as parts of their San Francisco plants are available and are being utilized by the community in the planned medical economy, with less expense to the local government and to the State Relief Administration than under another plan which would include setting up a new plant with overhead costs constituting a major item.

This same general statement of lowered costs to the relief agencies, due to already existing outpatient clinics maintained in the university hospitals, obviously holds true for the several other volunteer hospitals participating, on a contract basis, in the outpatient care of recipients of relief. The quality of their service, likewise, has been of high standard, and the service rendered has provided a real need in many instances because of religious and racial preferences. Here again the tolerant attitude has been manifest in the coördination of effort within the community so that the whole job might be done.

DISCUSSION

As mentioned previously, San Francisco possesses many advantages since it is recognized as a medical center. The ratio of one physician to less than 500 people in the city, with two outstanding medical schools, to-

gether with several approved voluntary hospitals, all make for a high standard of medical practice. This is a highly important unit in the community's resources in the medical care program, and the solution of community problems. Add to these advantages the official health and welfare agencies of the local and state government, in which there has been relatively high stability and efficiency of administration and adequate financing, with a high degree of integration of planning and action. Under this system any person needing emergency or non-emergency medical care can secure that care through existing channels and facilities.

This does not mean that the existing facilities in San Francisco are entirely adequate to meet all medical needs as they arise without delays. There are several inadequacies which should be emphasized. Some of these have been pointed out and others are probably apparent to the student of these problems.

Perhaps the most outstanding gap involves the recipients of public assistance for the aged, the blind, the dependent children, and those on work relief (WPA, NYA, CCC). While medical-dental-nursing services are available, in a planned program, for recipients of general relief, there is no planned program available to the group receiving these allowances, recognized in some respects to be liberal, but recognized also to be insufficient to provide adequate medical care. The voluntary outpatient clinics, supported in part by the Chest, have been very much interested in meeting the need and have attempted to provide outpatient care as best they could at part-pay and free rates. In many instances, too, privately practicing physicians have contributed to these persons without regard to a fee. Hospital or custodial institutional care to these people is available, however, as it is to the recipients of relief and the medically indigent of the population as a whole.

It is worthy of note, however, that there is a definite difference between the various types of medicine. Even a short term experience in the private practice of medicine impresses the physician with the difference between "hospital" practice and "private" practice; not as many, perhaps, are familiar with the third type which might be termed "relief" medicine. In the person unemployed, and without financial resources, the interrelations of his physical status, the mental stress resulting from his present condition, looking to the unavoidable change in standard of living on relief at public expense, the outlook toward his fellowman, his family, and himself, all assume an importance that is not as significant, usually, in private practice. In "relief" medicine, however, the frequency of such reactions and their definite effects is more nearly the rule than the exception. In dealing with such problems, in the medical area, valuable assistance to the physician can be had from the social worker and from the psychiatrist. It is unfortunate that in many instances the physician is reluctant to recognize the social worker's capacities as a possible resource of value to him in his work. Many sociologic factors of moment unknown to the physician are available to him through the social worker, if only he would recognize her accessibility.

From the administrative point of view another inadequacy deserves mention: standards of need, residence, and other factors affecting eligibility to relief and medical care are not uniform, with the result that investigation and reinvestigation, to the confusion and dismay of the applicant, are unavoidable. Too many separate agencies, with individually different standards, are involved in the whole program. Legislative instruments may be changed and thereby permit some simplification, but these will have to be rather extensive to accomplish the objective.

A third important inadequacy in the San Francisco set-up is that of facilities for convalescent care. With excessive demands made on the San Francisco Hospital, long waiting lists for eligible applicants for admission are created and the patient's stay in the hospital is shortened, sometimes to the point where it is medically unsound to discharge the patient, with the result that he is sent to his home earlier than good medical practice would dictate. Not infrequently the convalescent patient's home is one presenting inadequate housing and other hazards, forcing incomplete or delayed recovery. The need for convalescent care is recognized as a pressing problem, and it is hoped that augmentation of existing physical plants, particularly in the recently planned revamping of the rôle of the Laguna Honda Home and the Hassler Health Home in the whole program, will permit the development of better facilities for convalescent care in the near future.

SUMMARY

It must be apparent that certain desirable relationships between official and voluntary agencies exist in San Francisco. How have these relationships been developed? We believe that the answer to this question lies in three points which we have tried to bring out in this paper:

- (1) The type of government in force in San Francisco with a relatively high stability of administration;
- (2) The participation of the San Francisco County Medical Society in official and voluntary agencies' advisory boards and committees; and
- (3) The general attitude of civic minded persons interested in the community and participating in the study and solution of health, welfare, and related problems, some of the most consistent attributes of which are tolerance, a desire to get at the facts, and true unity of effort to solve the problem.

CONCLUSION

Though limitations of budget, of planning, and of coördination are effective, San Francisco has made significant strides toward achieving the integrated medical program. The fact is emphasized that the medically indigent in San Francisco are given high standard medical care at public expense.

This article endeavors to demonstrate that hospitalization for the acute

and the chronic ill, home visits by physicians, certain outpatient facilities such as for maternity and the tuberculous, follow-up surgical services especially as to fractures, emergency and ambulance services, generalized nursing in certain districts, infant welfare service of varied character, dental care for special groups, and nutritional services for needy school children are all furnished for the indigent by the Department of Public Health. This program is further integrated by the supplying of food and other needs for the family by the Relief organization and outpatient clinic facilities by the State-supported Central Medical Bureau and by a number of hospitals supported by the Community Chest. Certain limitations and inadequacies are admitted. The moot question, however, still remains unanswered: Can other departments of health and communities assume similar responsibilities, and further, can a voluntary insurance plan be adopted for certain low income groups which would cover hospitalization, medical care to include the nurse, the druggist, and the dentist, and family security care for the period of illness? The Department of Public Health spends each year \$4.228 per capita, the Community Chest \$0.677, the Relief Agency \$3.60, which includes the Central Medical Bureau, for this type of care for citizens of the City and County of San Francisco. This is a yearly per capita cost of \$8.505, which does not truly represent medical costs since attending and consultant Stanford and California Universities' staffs serve without compensation in several city and county institutions, as do other physicians in several hospitals and clinics financially supported in part by the Community Chest.

CASE REPORTS

CONGENITAL HEMOLYTIC JAUNDICE; REPORT OF A CASE OF CONGENITAL HEMOLYTIC JAUNDICE; INITIAL HEMOLYTIC CRISIS OCCURRING AT THE AGE OF 75; SPLENECTOMY FOL- LOWED BY RECOVERY *

By HARRY MANDELBAUM, M.D., *Brooklyn, New York*

CONGENITAL hemolytic jaundice presents several phases that deservedly attract wide interest. To the student of genetics there is offered a disease inherited as a true dominant character in accordance with the Mendelian principles of heredity (Naegli²¹). To the hematologist it affords the most classic example of true hemolytic anemia. To the internist the polymorphism of the presenting clinical picture, in many instances, differs so radically from the usual description of the disease as to tax his diagnostic acumen. However, the basic features are readily demonstrable and permit reasonable assurance in the diagnosis of congenital hemolytic jaundice. To the surgeon, splenectomy, the only remedial measure, offers a low operative hazard and is attended with exceedingly gratifying results.

Several names have been suggested to replace the usual one, "congenital hemolytic jaundice." Naegli²¹ suggested "spherocytic anemia"; Krumbhaar,¹⁸ "spherocytic icterus"; Whipple,²⁸ "typical hemolytic jaundice"; Fiessinger,⁷ "familial hemolytic splenomegaly"; and others.

Congenital hemolytic jaundice was first described by Murchison²⁰ in 1885. Its familial character was reported in 1890 by Wilson³⁰ and again in 1900 by Minkowski.¹⁷ Chauffard¹ in 1907 first directed attention to the microcytosis, increased fragility and reticulocytosis that characterize this disease and attributed the jaundice to active hemolysis. Naegli²¹ became the vigorous exponent of the hereditary nature of the condition; he described the decreased diameter and increased thickness of the characteristic microcytes. Haden⁹ measured this thickness and proved the close relationship between the point of initial hemolysis and the volume-thickness index.

Splenectomy offers the only cure for congenital hemolytic jaundice. It was first performed for this condition in 1907 by Vaquez and Giroux,²⁶ but the patient died. In 1911, Micheli¹⁶ reported a remarkable cure following splenectomy in a patient with familial hemolytic icterus. Lord Dawson⁴ credits Spencer Wales with having successfully performed splenectomy for hemolytic jaundice in 1887, without knowing the correct diagnosis at the time. At the Mayo Clinic, splenectomy has been done for this disease since 1911 (Pemberton²²).

The criteria for establishing the diagnosis of congenital hemolytic jaundice

* Received for publication July 5, 1938.

applied to a patient, aged 75, presenting evidence of increased blood destruction, led to its recognition. Splenectomy resulted in an immediate arrest of the hemolytic crisis and a remarkable recovery.

CASE REPORT

First Admission. Mrs. S. P., aged 75, was admitted to the Jewish Hospital of Brooklyn, January 13, 1937.

Past Personal History. Excepting childhood diseases, she had never been ill. She had never been jaundiced nor did she recall any history of jaundice affecting any of her relatives. She had always had a "sallow complexion."

Present Illness. Two weeks before admission she seemed to have lost her appetite completely. There was no nausea or vomiting, and no abdominal discomfort. Weakness and loss of weight necessitated her going to bed. After a week it was noted that she appeared more "sallow" than usual; there was no pruritus, the urine was not darker than usual and the stools were not clay-colored. A few days before admission headache appeared and increased in severity to such an extent that it dominated all other complaints when she entered the hospital.

Physical Examination. The patient appeared extremely weak. She was markedly anemic and obviously had lost considerable weight. The skin and sclera were slightly icteric; no scratch marks were seen. The heart by percussion measurements was slightly enlarged. The apical and radial pulse rate were 94. An extrasystole was noted every sixth or seventh beat. A rough systolic murmur was heard over the mitral area. The blood pressure was 132 systolic and 50 diastolic. The lungs showed nothing remarkable. The abdomen was soft. The liver was felt 3 cm. below the costal border; it was smooth and not tender. The spleen was felt 4 cm. below the costal border; it was firm and not tender. No masses or other organs were palpable. Neurologic examination was entirely negative.

Laboratory Summary. The urine concentrated well; no bile, albumin or sugar were reported. Urobilinogen was present in a concentration of 1:40 dilution units. The feces contained no ova or parasites; bile was present; in one specimen a trace of blood was detected. Roentgenologic survey of the gastrointestinal tract did not reveal any pathologic process. The gall bladder could not be visualized after double dye oral study. Gastric analysis (repeated twice) free HCl reached a concentration of 20; combined acidity, 36; blood was found in traces. Blood chemistry: sugar, 119 mg. per cent; urea nitrogen, 20 mg. per cent. Icteric index, 20. Van den Bergh, direct, biphasic; indirect, 4.1 units per 100 c.c. of serum. Blood count: red cells, 1,920,000; hemoglobin, 38 per cent; color index almost one; white cells, 3,700; platelets appeared to be present in less concentration than normally. Morphologic blood study: neutrophils, 51 per cent; eosinophils, 1 per cent; lymphocytes, 45 per cent; monocytes, 3 per cent; reticulocytes, 1.8 per cent; marked anisocytosis and poikilocytosis, positive hyperchromia, moderate number of macrocytes and microcytes; no punctate basophilia, no nucleated reds. Bleeding time, two minutes; tourniquet test, positive; coagulation time, 3 minutes. Fragility test: normal (see table 4).

Course. Repeated blood studies suggested pernicious anemia, but the presence of free HCl in the gastric juice definitely ruled this out. No evidence of malignancy was obtained. The occasional microcyte, while suggestive, was not conclusive in the presence of normal fragility. Liver extract was given parenterally, daily. Five days after admission, the reticulocyte count* increased to 12 per cent, the hemoglobin increased to 42 per cent; the red blood cells totaled 2,200,000; color index, 0.95. Patient was discharged January 27, 1937.

Second Admission. Mrs. P. was readmitted to the Jewish Hospital July 19, 1937.

*The reticulocyte increase occurred 48 hrs. after the first injection of liver extract.

After her discharge from the hospital she had been given (by her son, a physician) injections of liver extract once a week for two months. She gradually regained her weight and strength. A month before readmission her son observed that she had again lost her appetite; she became weak, lost weight, and complained of headache. She appeared anemic and slightly jaundiced. Liver extract was injected daily, but the anemia progressively increased, headache became unbearable and general weakness marked. There was no abdominal pain, nausea or vomiting. Dyspnea and palpitation followed slight effort, and ankle edema appeared upon dependency.

Physical examination. Mrs. P. appeared extremely weak and emaciated. Anemia was marked. The skin and sclera were icteric ++; no scratch marks were visible. Moderate orthopnea was present; the percussion outline of the heart was enlarged; the sounds were of poor muscular tone; a soft mitral systolic murmur was heard; many extrasystoles were noted. The apical rate was 100; the blood pressure was 118 systolic and 74 diastolic. Coarse râles were evident over both bases. Ankle and sacral edema were present. The abdomen was soft. The liver was felt 7 cm. below the costal arch and was tender. The spleen was felt 6 cm. below the costal edge, was firm and not tender.

Laboratory Summary. The urine showed no bile, albumin or sugar; urobilinogen was reported in a concentration of 1:40 dilution units. The feces showed bile, and traces of blood were occasionally found. Blood chemistry: sugar, 108 mg. per cent; urea nitrogen, 10.5 mg. per cent; cholesterol, 376 mg. per cent. Icteric index, 25. Van den Bergh, direct, biphasic; indirect, 10 units per 100 c.c. of serum (for further studies see table 3). Roentgen study of the long bones failed to reveal findings suggestive of metastatic malignancy. Blood count on admission: red cells, 1,320,000; hemoglobin, 30 per cent; color index, 1.1; white cells, 5,400. Morphologic blood study: neutrophils, 80 per cent; lymphocytes, 20 per cent; moderate anisocytosis, poikilocytosis and polychromatophilia; macrocytes ++; microcytes, ++; no nucleated red cells; reticulocytes 28.6 per cent; fragility increased (table 4).

Course. Five hundred cubic centimeters of whole blood were transfused on July 21, and again on July 26. As shown in table 1, the hemolysis continued so actively

TABLE I
During an Acute Hemolytic Crisis, Transfusion Effects But a Brief Check to the Advancement of the Anemia.

Date 1937	Hemoglobin Sahli	Erythrocyte count	Color index	Leukocyte count
July 19	30%	1,320,000	1.1%	5,400
July 21		Transfusion 500 c.c. citrated blood		
July 23	37%	1,680,000	1.1%	9,400
July 26		Transfusion 500 c.c. citrated blood		
July 27	35%	1,430,000	1.2%	9,500
July 28	34%	1,340,000	1.3%	5,200

that each transfusion effected but a temporary respite from the increasing anemia. The presence of acute hemolytic anemia, acholuric jaundice without pruritus, bilirubinemia, increased urobilinogen in the urine and characteristic Van den Bergh reactions; a microcytosis in the presence of marked anemia, with attendant increased fragility to hypotonic salt solutions; reticulocytosis; and splenomegaly, were dependable criteria for establishing the diagnosis of congenital hemolytic jaundice in the stage of acute hemolytic crisis. Splenectomy was suggested as the only measure available. Daily transfusions of 300 c.c. of citrated blood were given, and when the hemoglobin was brought up to 56 per cent and the red blood cells to 2,700,000, she was considered a safe surgical risk (table 2).

TABLE II

Preoperative and postoperative blood studies. Note difficulty in raising the hemoglobin and red blood cell values before splenectomy. Within three days after operation, the concentration of red blood cells was increased by over a million. The effect of a number of complications accompanied by pyrexia was a gradual lowering of the hemoglobin and erythrocyte concentration. Compare the immediate response following transfusion October 1 with that shown in table 1.

Date 1937	Hemoglobin Sahli	Erythrocyte count	Leukocyte count	Poly. neut.	Eosin.	Lymph.	Mono.	Addenda
Aug. 4	23%	900,000	4,700	55%	2%	47%	1%	Retic. 39.3%
Aug. 4		Transfusion 300 c.c. citrated blood.						
Aug. 5		Transfusion 300 c.c. citrated blood.						
Aug. 6		Transfusion 300 c.c. citrated blood.						
Aug. 7	40%	1,780,000						
Aug. 7		Transfusion 300 c.c. citrated blood.						
Aug. 8		Transfusion 300 c.c. citrated blood.						
Aug. 9		Transfusion 300 c.c. citrated blood.						
Aug. 9	53%	2,470,000						Coag. time 2 min.
Aug. 10		Transfusion 300 c.c. citrated blood.						
Aug. 10	53%	2,230,000						
Aug. 11		Transfusion 300 c.c. citrated blood.						
Aug. 11	56%	2,700,000						
Aug. 12		Preoperative transfusion 300 c.c. citrated blood.						
Aug. 13	67%	2,640,000	6,100	85%		15%		Retic. 20% Platelets 145,000
Aug. 14	70%	2,960,000	9,850	92%	2%	6%		
Aug. 16	70%	2,850,000	8,800	93%		7%		Retic. 2.3%
Aug. 17	70%	3,180,000	7,800					
Aug. 19	67%	3,450,000	7,600	82%		16%	2%	Microcytes++
Aug. 20	70%	3,850,000	9,450	72%	2%	20%	6%	Retic. 1.8%
Aug. 21	67%	3,850,000						
Aug. 24	70%	3,450,000	8,100					
Aug. 25	59%	3,090,000	8,850					Acute cholecystitis.
Aug. 28	60%	2,780,000						
Aug. 29	59%	2,900,000						
Aug. 30	53%	2,330,000						
Aug. 31	50%	2,690,000	7,800	58%	8%	26%	8%	Microcytes++
Sep. 1	56%	3,550,000						
Sep. 2	50%	2,240,000						Onset of phlebitis.
Sep. 3	56%	2,280,000	9,800	70%	4%	21%	4%	1% myelocytes
Sep. 5	54%	2,300,000						
Sep. 8	51%	2,550,000	9,100	54%		38%	8%	
Sep. 14	62%	2,310,000	7,500	78%	2%	18%	2%	
Sep. 20	54%	2,750,000	17,400	78%	1%	19%	2%	Acute cystitis.
Sep. 22	50%	2,660,000	13,100	76%	3%	16%	5%	Microcytes++
Sep. 27	46%	2,690,000	10,200	48%	5%	32%	10%	
Sep. 30	53%	2,570,000	14,700					
Oct. 1		Transfusion 300 c.c. citrated blood.						
Oct. 2	70%	3,670,000						
Oct. 6	65%	3,330,000	12,500	59%	8%	27%	1%	5% basophiles
Oct. 12	56%	2,960,000	6,500	40%	5%	51%	3%	1% basophiles
Nov. 3	65%	3,400,000	11,300	33%	8%	48%	9%	2% basophiles
Mch. 28, 1938	60%	2,900,000	9,400	38%	5%	55%	2%	Retic. 2%
May 17, 1938	68%	3,300,000	16,400	45%	5%	36%	11%	3% basophiles Retic. 1%

Operation. Dr. B. Kogut, August 12, 1937. Avertin and ether anesthesia. On opening the peritoneum there was an escape of some thin serous fluid. The uterus was small. The stomach appeared normal and careful palpation failed to reveal any lesion. The gall bladder was enlarged and tense; no stones were palpable. The pancreas was essentially normal. The liver was somewhat enlarged; many fibrous streaks were present, giving the liver a gray color. The spleen was considerably enlarged, about three times its normal size; many fibrous strands were evident. A small accessory spleen was found just posterior to the hilus of the spleen proper. The spleen and accessory spleen were removed.

Pathological report. Dr. Max Lederer. The specimen consists of a spleen 18 by 13 by 6 cm., weighing 650 gm. The external surface is purple and roughened by delicate pink tags. There is a raised yellow area, 1.5 by 1 cm. The cut surfaces are brown-red; the Malpighian corpuscles and fibrous markings are prominent. The pulp does not scrape easily. The raised yellow area, above described, extends 1.2 cm. below the external surface. The accessory spleen measures 2 cm. in diameter and has the general characteristics of the spleen proper. Microscopic study: The trabeculae of the spleen appear thickened. The Malpighian bodies are fairly large and well spaced; some have active germinal centers. There is an increase in the reticulo-endothelial elements. The sinusoids are distended and their lining cells prominent; some are empty, others contain a large number of red blood cells, large mononuclear cells, eosinophiles and a few polymorphonuclear leukocytes. Occasional megakaryocytes are seen. Scattered throughout the preparation is a great deal of golden brown pigment; this is both extracellular and intracellular (contained within large mononuclear cells). With the Perl stain, this pigment is seen to contain iron. Sections through the raised yellow area described above show zones in which only a faint outline of the former cytoarchitecture is seen. In and about these zones there is round cell infiltration. Diagnosis: The histologic picture is compatible with the diagnosis of congenital hemolytic jaundice; a small infarct is present.

Postoperative course. The patient reacted well for the first 24 hours; then auricular fibrillation was noted, with an apical rate of 120 and a radial pulse of 110. The blood pressure remained about 120 systolic and 80 diastolic during this period and continued so throughout her hospital stay. The heart responded well to digitalis. The temperature rose to 102° F. postoperatively and continued at about this level for 36 hours; then it ranged between 100° F. and 101° F. for the succeeding 12 days. On August 20 (eight days postoperatively), examination of the lungs showed dullness, diminished breathing, and fine crepitant râles over the left base. Two days later physical signs of a left pleural effusion, reaching to the inferior angle of the scapula, were obtained; the heart was displaced slightly to the right. The heart rate was maintained at 78; auricular fibrillation was still present; there was no pulse deficit; the cardiac sounds were of good quality; sacral edema was slight. Resorption of the effusion was complete by August 25, at which time the jaundice had appreciably decreased; the heart was no longer fibrillating; an occasional extrasystole was present; there was no sacral edema; the liver edge was palpated at the costal border. That evening (August 25), the patient complained of abdominal pain and vomited. The temperature rose to 102.4° F. The following day the gall bladder could be felt, distended and tender; the jaundice again deepened; the icteric index increased from 13.3 to 31.5 (see table 3) and bile appeared in the urine for the first and only time. The temperature continued intermitting up to 102° F. until August 28, then ranged between 99° F. and 100° F. for the next three days; epigastric pain continued and repeated vomiting necessitated parenteral saline injections to maintain water and electrolyte balance. By September 3 abdominal pain and vomiting had ceased, the gall bladder was no longer palpable, and the jaundice was receding.

During the next three weeks (September 1 to September 21), the temperature

ranged between 99° F. and 102° F. daily. Phlebitis of the left internal saphenous vein had developed; the vein was exquisitely tender in the middle third of the thigh, with edema extending from the middle of the thigh to the base of the toes. Blood cultures taken during this period were subsequently reported negative. Ice bags were applied to the vein and the leg was elevated; edema and tenderness gradually abated.

From September 21 to October 1 the temperature did not rise above 101° F. An acute cystitis developed; dysuria and frequency disturbed the patient considerably. Mandelic acid therapy effected a cure.

The succession of complications had rendered the patient weak and exhausted. A transfusion of 300 c.c. of blood was given October 1, the first since her operation. She improved rapidly. The temperature remained normal after October 4; she was permitted out of bed after another week and discharged from the hospital October 13, 1937.

TABLE III

Icteric index and Van den Bergh studies. Sharp rise on August 27 was associated with symptoms and physical signs of gall bladder affection.

	Date 1937	Icteric Index	Van den Bergh	
			Direct	Indirect
Pre-operative	July 21	24.2		
	July 26	25	Biphasic	10 units
Postoperative	Aug. 16	14.3		
	Aug. 20	13.3		
	Aug. 23	13.3		
	Aug. 27	31.5	Biphasic	4.1 units
	Aug. 30	23	Biphasic	5.1 units
	Sep. 2	22.2	Biphasic	4.4 units
	Sep. 9	14.2	Biphasic	4.8 units
	Sep. 13	16.4	Biphasic	4.8 units
	Sep. 17	14		
	Oct. 6	13.8	Biphasic	4 units
	Oct. 12	14		

Subsequent course. Following her discharge from the hospital she continued to improve, gradually regaining her weight and strength. She resumed her customary activity. There has been no recurrence of the biliary dyspepsia. She has maintained (without hematinics) a hemoglobin above 65 per cent and a red blood cell count above 3,000,000. Blood count and morphologic studies done May 17, 1938 (nine months postoperative) showed the following: red cells, 3,300,000; hemoglobin, 68 per cent; white cells, 16,400; neutrophils, 45 per cent; eosinophils, 5 per cent; lymphocytes, 36 per cent; monocytes, 11 per cent; basophils, 3 per cent; moderate chromatophilia, slight anisocytosis, few macrocytes, moderate number of microspherocytes and one nucleated red cell; reticulocytes, 1 per cent. Increased fragility of the red cells was still present (see table 4). Icteric index, 7 (May 18, 1938).

DISCUSSION

Congenital hemolytic jaundice is an inherited familial disease. It can occur in either sex of any race at any age. While most cases give rise to symptoms leading to their recognition in early adult life (Kracke and Garver¹²), cases

TABLE IV

Fragility tests done on patient and control. Creed² has shown that anemia of itself increases the resistance to hypotonic salt solutions and must be taken into account in interpreting the fragility curves.

Date	Unwashed Cells				Washed Cells			
	Patient Hemolysis		Control Hemolysis		Patient Hemolysis		Control Hemolysis	
	begins	complete	begins	complete	begins	complete	begins	complete
1-14-37	0.46	0.36	0.46	0.34	0.46	0.32	0.46	0.34
8-9-37	0.60	0.38	0.46	0.32	0.56	0.44	0.46	0.34
8-25-37	0.52	0.38	0.46	0.34	0.52	0.38	0.46	0.32
10-14-37	0.52	0.32	0.44	0.34	0.52	0.32	0.44	0.32
5-18-38	0.50	0.34	0.44	0.32	0.50	0.34	0.44	0.32

have been recognized at birth (Gänsslen⁸); in Thompson's series,²⁵ the youngest was six weeks and the oldest, 58 years.

Clinical features. The outstanding characteristics of congenital hemolytic jaundice are the chronic acholuric (dissociated) jaundice without pruritus, persistent enlargement of the spleen and hemolytic anemia. In many cases there is an overemphasis of one or the other of the cardinal features: the splenomegaly may be out of proportion to the degree of anemia and jaundice; the spleen may occupy the greater part of the abdomen and extend to the pelvic brim. Pigment stones, which are frequently present in this disease (68.6 per cent of the cases reported by Pemberton²²), may lead to gall stone colic and obstructive jaundice. The anemia is usually of the hyperchromic type and may be mistaken for pernicious anemia, especially when the color index is above one and an abundance of red blood cells, larger than normal erythrocytes, are seen; most of these large cells may be identified as reticulocytes when brilliant cresyl blue is used as a vital dye (Thompson²⁵).

The pathognomonic findings in congenital hemolytic jaundice. (a) The microspherocyte: The basic cellular change in this disease is the presence of specific red blood cells which are characteristically more spheroid in shape, their diameter smaller than normal, and their thickness greater than normal. The volume-thickness index of Haden is increased. They vary in number and it is thought that their sudden increase in the blood stream may lead to increased activity of the spleen and result in an acute hemolytic crisis. Haden,⁹ Thompson,²⁵ Krumbhaar¹³ and others have stated their conviction that the microspherocyte is an inherited variant from normal. It is frequently associated with other anomalies, such as the "tower skull" described by Gänsslen.⁸ (b) The increased fragility of the red blood cells: Haden⁹ has conclusively proved the relationship between the size and shape of the red cells (the volume-thickness index) and their hemolytic reaction to hypotonic saline solutions. His work leaves no doubt that the spherical microcytes alone are responsible for the increased fragility that characterizes congenital hemolytic icterus.

The rôle of the spleen. The spleen is an area of concentration along the line of the reticulo-endothelial system. Under physiologic conditions there is main-

tained in health a balance between bone marrow hematopoiesis and the splenic function of cell storage and cell destruction; the term hemolytopoietic balance was suggested by Krumbhaar.¹⁴ It is believed that the presence of microspherocytes in the circulating blood stimulates the spleen to increased activity. Klemperer¹¹ believes this to be due to a reflex mechanism resulting in an active hyperemia of the spleen that leads to hyperplasia. The spleen becomes enlarged and markedly hyperemic; there is striking engorgement of the reticular meshes of the red pulp. This engorgement provides the opportunity for increased blood destruction by the macrophages of the splenic pulp. To maintain a hemolytopoietic balance, the bone marrow increases its erythrogenic activity; this is evidenced in the peripheral blood by reticulocytosis, leukocytosis, anisocytosis, polychromasia and the presence of nucleated red blood cells. In the presence of a severe hemolytic crisis, the bone marrow is stimulated to even greater activity; this is reflected in the myelogram (table 5), which shows a marked increase in

TABLE V

Myelogram and concomitant blood smear studies by Dr. M. Morrison. Note marked hyperactivity in erythropoiesis as revealed by the bone marrow smear preoperatively.

			Normal values	Preoperative Aug. 6, 1937	Postoperative Sep. 10, 1937
Bone Marrow Smears	Granulocytes	Myeloblasts	0-5%	11%	1%
		Myelocytes	25-36%	22%	42%
		Metamyelocytes	5-10%	6%	4%
		Eosinophilic myelocytes	0-1%	2%	4%
		Staff cells	0-5%	26%	10%
	Lobocytes	Polymorphonuclear neutrophiles	45-50%	26%	35%
		Eosinophiles	0-1%	7%	3%
		Lymphocytes	5-10%	0%	1%
		Monocytes	1-2%	0%	0%
		Granulocyte : lobocyte ratio	55 : 45	67 : 33	61 : 39
		Granulocyte : erythroid ratio	90 : 10	15 : 85	68 : 32
		Early : late cell ratio	10 : 90	60 : 40	50 : 50
Concomitant Blood Smears		Polymorphonuclear neutrophiles		70%	72%
		Eosinophiles		2%	0%
		Staff cells		0%	6%
		Lymphocytes		22%	18%
		Monocytes		6%	4%
		Anisocytosis		++++	++
		Poikilocytosis		++++	++
		Polychromasia		+++	+
		Macrocytes		+	+
		Microcytes (spherical)		++	++

the erythrogenic function of the bone marrow, and in the hemogram, where young red cells are in abundance; a reticulocytosis (up to 50 per cent) and a marked leukocytosis (as high as 50,000) have been reported.

Clinical course. In some, symptoms are manifest at birth; in others, the disease may not appear until early childhood or adult life; in still others, it may never appear in such outspoken form as to be recognized (Gänsslen⁸). Such latent cases may never show clinical symptoms of the disease and may live active lives; many show a peculiar pallor which is usually considered to be their natural

color. The blood of these patients shows the characteristic microspherocytes and exhibits the increased fragility reactions. Little is known about those factors which initiate the excessive hemolysis that signals the onset of the active disease. The latent cases may become active at any time during their life; in Thompson's cases,²⁵ the age at which activity began varied from six months to 59 years. Once the disease becomes active, spontaneous remissions and recurrences alternate and chronic anemia and jaundice persist until splenectomy. These recurrences (acute hemolytic crises) interrupt the otherwise placid course of the disease and are characterized by an acute onset with rapidly increasing anemia and jaundice; the degree of anemia and bilirubinemia are proportionate to the extent of red blood cell destruction; the spleen increases in size, indicative of its increased activity; the urine and feces show an increased excretion of urobilinogen.

Treatment. Splenectomy is generally accepted as the only remedial measure applicable to cases of congenital hemolytic jaundice. It is indicated when the diagnosis is established. It has proved most valuable as an emergency measure in critical severe hemolytic anemias (Doan and his associates⁵). It removes a large part of the erythro-phagocytic mechanism and permits the maldeveloped erythrocyte to remain and function longer in the circulating blood; the bone marrow is thus better able to contribute its physiologic rôle to the hemolytotoxic balance. Splenectomy effects immediate relief; the already overactive bone marrow rapidly raises the concentration of the circulating red blood cells. Moore and Doan¹⁹ observed an immediate postsplenectomy rise of a million erythrocytes; they attributed this to contraction of the spleen. The hemogram, after splenectomy, continues to show microspherocytes and young red blood cells, but in less concentration; the increased fragility, while not as marked as previously, never completely disappears. Lord Dawson,³ in referring to the case operated upon by Spencer Wales in 1887, stated that he had been able to demonstrate increased fragility in this patient 27 years later. Splenectomy does not remove the inherited abnormality, the faulty red blood cell. Lord Dawson⁴ reported that he had observed cases where removal of the spleen was ineffective and increased blood destruction continued. It is advisable, at operation, to search for accessory spleens, and to remove them, if found. This is as applicable in congenital hemolytic jaundice as it has been proved to be in essential thrombocytopenic purpura (Morrison and associates¹⁸).

Acquired hemolytic jaundice. The so-called acquired form of hemolytic jaundice was first described by Widal²⁹ in 1907. It covers a number of hemolytic conditions of varied nature. Most competent authorities doubt the existence of an acquired type. Whipple and his associates²⁸ classify their cases of hemolytic jaundice as typical and atypical. The typical group conformed to the criteria pathognomonic of congenital hemolytic jaundice. In the atypical group reported by Thompson,²⁵ there were 15 cases. Four, all elderly, were proved to have reticulum cell sarcoma of the spleen. Two patients presented the syndrome in association with positive blood Wassermanns; antiluetic treatment cured them. One case at autopsy showed extensive tuberculosis with active involvement of the spleen. Four other cases had submitted to splenectomy, without improvement. Kracke and Garver¹² consider the so-called acquired cases of hemolytic jaundice as true latent cases which have become activated by intercurrent infection, trauma, tuberculosis, syphilis, malaria, etc. Meulengracht,¹⁵ however, be-

lieves that acquired hemolytic jaundice is an entity. He reported three cases in patients past 40 who presented all the clinical features of the disease. In none of these patients were any spherical microcytes present, although the red blood cells showed increased fragility to hypotonic salt solutions. He attributed the pathogenesis in these cases to the spleen and reported recovery following splenectomy.

Case discussion. The problem presented for diagnosis was one of hemolytic anemia with jaundice and splenomegaly. The degree of anemia, the leukopenia, the slight icterus, the color index of 1.0, a palpable spleen and the abundance of macrocytes were suggestive of pernicious anemia; the presence of free HCl removed this possibility from further consideration.

The general appearance suggested malignancy. It is well recognized that profound changes often take place in the blood of patients suffering from malignant tumors with extensive metastasis to the bone marrow. Waugh²⁷ reported cases where severe hemolytic anemia was present. Kiser and Rosenak¹⁰ reported a similar case. Roentgenologic investigation of the gastrointestinal tract and long bones in the present case failed to reveal any suspicion of malignancy.

The morphologic blood studies done on the first admission were not conclusive; microcytes were not prevalent, the percentage of reticulocytes was slightly increased, and the fragility test was normal. Scott²³ has observed that during an acute hemolytic crisis the reticulocyte count may be low, rising sharply after the crisis had passed. Thompson²⁴ noted that while the fragility was increased in most cases of congenital hemolytic jaundice it varied in degree in different persons and in the same person at different times. He reported a case where the fragility was normal before splenectomy and only after operation was the characteristic increased fragility obtained. Doan, Curtis and Wiseman⁵ also state that microcytosis, reticulocytosis and increased fragility changes may not be present during the acute crisis.

Krumbhaar,¹³ Kracke and Garver¹² and Thompson²⁵ concur in the observation that while the hemolytic tendency in patients with congenital hemolytic jaundice may remain latent for years, once activity has become manifest, spontaneous remissions are common. Thus a remission occurring spontaneously five months after hemolytic anemia had first appeared suggested a diagnosis of typical rather than atypical hemolytic jaundice. Many microcytes were noted in the morphologic blood study and their spherical shape recognized in wet preparations. The increased fragility of the red blood cells to hypotonic salt solutions added security and confidence to the diagnosis of congenital hemolytic jaundice. The severity of the hemolytic crisis made it imperative to remove the offending spleen, despite the age of the patient. The remarkable success that splenectomy achieved was most gratifying. Subsequent blood studies (the last was taken eight months postoperatively) showed microspherocytes still to be present, but in less concentration, and the attendant increased fragility likewise present.

SUMMARY

A case of congenital hemolytic jaundice has been presented. The disease remained latent until the patient had passed the seventy-fifth year; then activity was first manifested in an attack of acute hemolytic anemia. A recurrence occurred five months later, with alarmingly increasing anemia.

In the presence of a true hemolytic anemia, the identification of spherical microcytes and the demonstration of their increased fragility to hypotonic saline solutions may be considered pathognomonic of congenital hemolytic jaundice. These findings formed the basis for establishing the diagnosis in this case.

In the presence of a severe hemolytic crisis, splenectomy offers the only measure that can promptly terminate the excessive red blood destruction. The remission that splenectomy effected in this case was truly remarkable.

The demonstration of characteristic spherical microcytes, and their attendant increased fragility to hypotonic salt solutions, eight months after splenectomy, serves again to emphasize the true constitutional nature of the defect in the red blood cells that characterizes congenital hemolytic jaundice.

Note. Patient died 18 months after operation, from cerebral apoplexy.

BIBLIOGRAPHY

1. CHAUFFARD, M. A.: Pathogénie de l'ictère congénital de l'adulte, *Semaine médicale*, 1907, xxvii, 25.
2. CREED, C. F.: Estimation of fragility of red blood corpuscles, *Jr. Path. and Bact.*, Edinburgh, 1938, xlv, 331.
3. DAWSON, LORD: Hemolytic jaundice, *Proc. Roy. Soc. Med., Clinical Section*, 1913-1914, vii, 101.
4. DAWSON, LORD: Indications for and results of removal of spleen, *Brit. Med. Jr.*, 1932, ii, 699.
5. DOAN, C. A., CURTIS, G. M., and WISEMAN, B. K.: The hemolytic equilibrium and emergency splenectomy, *Jr. Am. Med. Assoc.*, 1935, cv, 1567.
6. EPPINGER, H.: *Die hepato-lienalen Erkrankungen*, 1926, Julius Springer, Berlin.
7. FIESSINGER, N.: Société médicale des hôpitaux de Paris. Report of May 15, 1936 meeting, *Jr. Am. Med. Assoc.*, 1936, cvii, 513.
8. GÄNSSLEN, M.: Hemolytic jaundice, *Deutsch. Arch. f. klin. Med.*, 1922, cxl, 210.
9. HADEN, R. L.: The mechanism of increased fragility of the erythrocyte in congenital hemolytic jaundice, *Am. Jr. Med. Sci.*, 1934, clxxxviii, 441.
10. KISER, E. F., and ROSENAK, B. D.: Myelophthisic anemia in a case of carcinoma of the stomach, *Jr. Am. Med. Assoc.*, 1936, cvii, 963.
11. KLEMPERER, P.: The pathologic anatomy of splenomegaly, *Am. Jr. Clin. Path.*, 1936, vi, 99.
12. KRACKE, R. R., and GARVER, H. E.: *Diseases of the blood and atlas of hematology*, 1937, J. B. Lippincott Company, Philadelphia.
13. KRUMBHAAR, E. B.: Hemolytic jaundice. Spherocytic icterus, *Jr. Am. Med. Assoc.*, 1936, cvii, 1739.
14. KRUMBHAAR, E. B.: The hemolytopoietic system in the primary anemias with a further note on the value of splenectomy, *Am. Jr. Med. Sci.*, 1923, clxvi, 329.
15. MEULENGRACHT, E.: *Handbook of hematology*. Edited by Hal Downey, 1938, Paul B. Hoeber, New York, p. 2283.
16. MICHEL, F.: Unmittelbare Effekte der Splenektomie bei einem Fall von erworbenem Ikterus. Typus Hayem-Widal, *Wien. klin. Wchnschr.*, 1911, xxiv, 1269.
17. MINKOWSKI, O.: Über eine hereditäre unter dem Bilde eines chronischen Ikterus mit Urobilinurie, Splenomegalie und Nierensiderosis verlaufende Affection, *Vrhandl. d. Kong. f. inn. Med.*, Wiesbaden, 1900, xviii, 316.
18. MORRISON, M., LEDERER, M., and FRADKIN, W. Z.: Accessory spleens. Their significance in essential thrombocytopenic purpura hemorrhagica, *Am. Jr. Med. Sci.*, 1928, clxxvi, 672.
19. MOORE, C. V., and DOAN, C. A.: Mechanism of post-splenectomy erythroid reequilibration, *Jr. Am. Med. Assoc.*, 1936, cvi, 325.

20. MURCHISON, C.: Clinical lectures on diseases of the liver and jaundice. Edited by L. Brunton, London, 3rd Edition, 1885.
21. NAEGLI, O.: Blutkrankheiten und Blutdiagnostik, 1931, Julius Springer, Berlin.
22. PEMBERTON, J. J.: Results of splenectomy in splenic anemia, hemolytic jaundice and hemorrhagic purpura, *Ann. Surg.*, 1931, xciv, 755.
23. SCOTT, A. M.: Acholuric jaundice, *Lancet*, 1935, ii, 872.
24. THOMPSON, A. P.: Acholuric jaundice and increased fragility of the red blood corpuscles appearing after splenectomy, *Lancet*, 1933, ii, 1139.
25. THOMPSON, W. P.: Hemolytic jaundice, *Jr. Am. Med. Assoc.*, 1936, cvii, 1776.
26. VAQUEZ, H., and GIROUX, R.: Ictere chronique acholurique avec splenomegalie; ses relations avec l'anémie hemolytique, *Bull. et mém. Soc. méd. d. hôp. de Paris*, 1907, xxiv, 1184-1192.
27. WAUGH, T. R.: Hemolytic anemia in carcinomatosis of the bone marrow, *Am. Jr. Med. Sci.*, 1936, cxc, 160.
28. WHIPPLE, A. O.: Studies in splenopathy, *Jr. Am. Med. Assoc.*, 1936, cvii, 1775.
29. WIDAL, F., ABRAMI, P., and BRULE, M.: Pluralité d'origine des ictères hemolytiques recherches cliniques et expérimentelles, *Bull. et mém. Soc. méd. d. hôp. d. Paris*, 1907, xxvii, 1354-1367.
30. WILSON, C.: Hereditary enlargement of the spleen, *Brit. Med. Jr.*, 1890, i, 782. *Lancet*, 1890, i, 751.

HISTOLOGICALLY NON-MALIGNANT METASTASIZING HEMANGIOMA, WITH REPORT OF A CASE*

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THE rarity of this condition might not alone be sufficient reason for reporting a case, were its interest not heightened by the unusual and misleading diagnostic problem presented.

CASE REPORT

The patient was a white man, 35 years old, who was admitted to the Medical Service of the University Hospital on January 19, 1932. The circumstances prompting his admission will be described later.

His father died of tabes at 49 years; his mother was living and outwardly well at 60 years of age, though her Wassermann reaction was four plus. Her first two children were stillborn and the patient was her third child. During his infancy he apparently had congenital syphilis which was manifested by desquamation, bullae and loss of nails. Though untreated, he survived, and with the exception of a swelling of the right testicle at 10 years, his childhood and adolescence were not remarkable.

He was married at 21 years of age, and an only child was born one year later. The Wassermann reaction of this child at the present time is negative.

A review of his past history reveals positive findings only in the respiratory and gastrointestinal systems. In 1918, at 21 years of age, he developed a slight hacking cough which was unproductive and not associated with loss of weight, fever, night sweats, or chest pains. This cough persisted unchanged until 1923 when hemoptysis and productivity appeared. The hemoptyses were consistent but very slight, being described by the patient as "only a drop or two with each expectoration." The amount of blood, however, gradually increased, so that every productive cough brought

* Received for publication April 11, 1938.

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up sufficient blood to distinctly color the sputum. There were occasional remissions never exceeding three days, during which his cough became minimal and the sputum almost blood free.

In 1927, nine years after the onset of the cough, and four years after the beginning of his hemoptyses he first experienced pain in his chest. The pain was bilateral,



FIG. 1. Roentgen-ray of the chest taken in 1925 (seven years prior to admission). Note annular shadow in right hilic region.

was increased with deep inspiration and cough, and would persist for several weeks with remissions of several months. At this time, the patient was under the care of his family physician, at whose direction a roentgenogram was made (figure 1). This film shows near the right pulmonary hilus a rounded mass of even consistency unassociated with other parenchymal changes.

It was just at this time that the patient's father died of tabes, and that the patient himself was found to have a four plus Wassermann reaction. Anti-syphilitic treatment was carried on for one year. While his Wassermann reaction never became negative, a roentgenogram of the chest one year later (figure 2) shows the dis-



FIG. 2. Roentgen-ray of chest one year later. Note annular shadow is replaced by increase in fibrous tissue structure.

appearance of the annular shadow with marked increase in the fibrous structure of the right lower lobe. On admission to the hospital (seven years after the original plate) the changes in the right lower lobe are even more striking, with tremendous increase in the fibrotic changes. (Figure 3.)

In his gastrointestinal history, one incident that occurred nine years before de-

serves comment. At that time he says that everything he swallowed caused excruciating pain in the right upper quadrant near the midline. This sensation lasted about 10 days and disappeared entirely. Two months prior to admission the patient himself noticed an abdominal mass, but he was quite unconcerned about it.

He was admitted to the hospital after having been apprehended while in the act

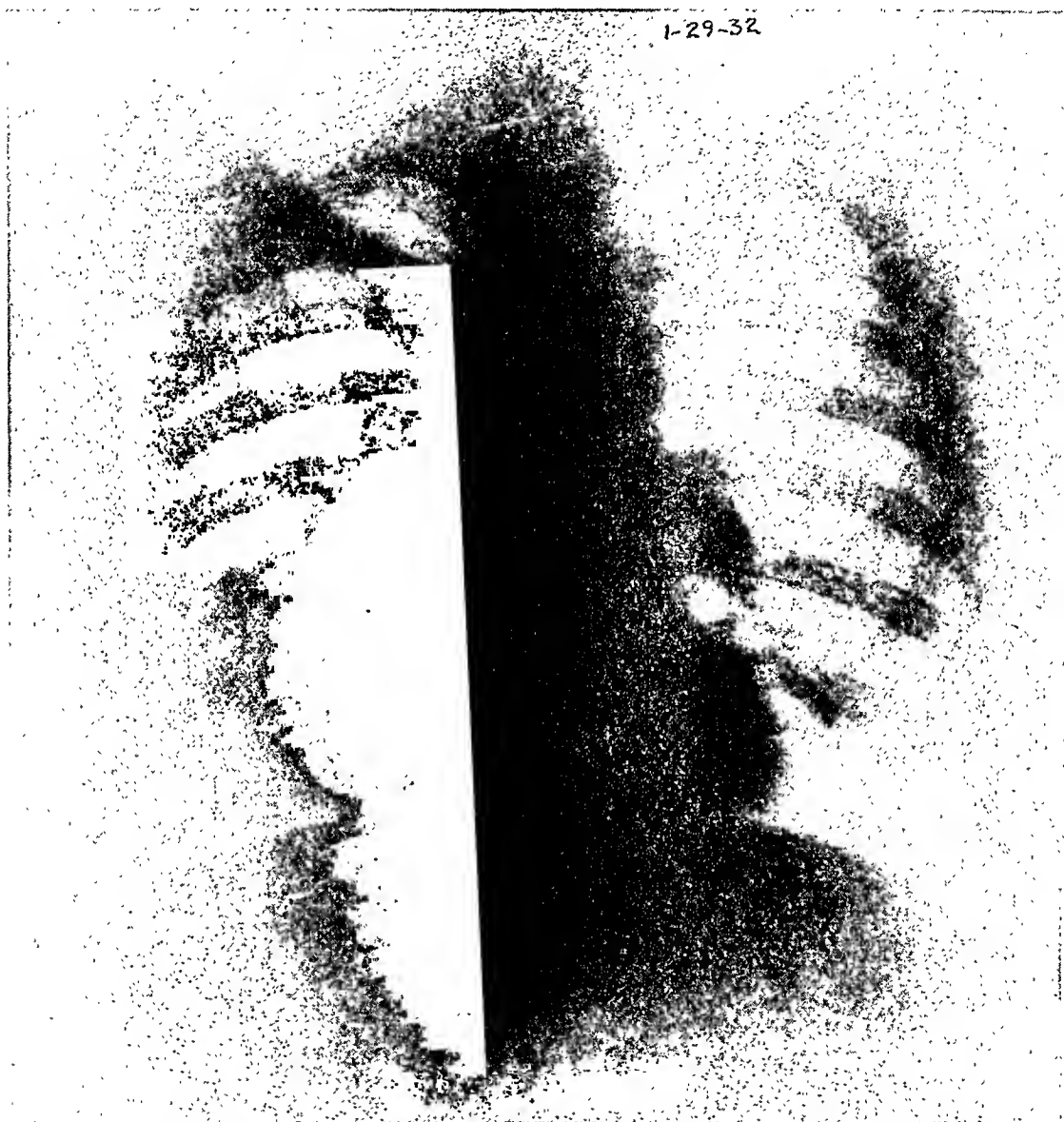


FIG. 3. Roentgen-ray of chest taken on admission seven years after figure 1. Note fibrous tissue proliferation in right hilic region, more marked than in figure 2.

of walking off a wharf. He claimed there was no suicidal intent, that everything seemed clouded and that he just could not stop himself. This incident was responsible for his hospitalization.

The physical examination revealed the following positive findings. In the chest over the right lower lobe there was increased tactile fremitus, impairment of the percussion note, and broncho-vesicular breathing with persistent fine râles.

The abdomen revealed a large firm mass which extended diagonally from above the costal margin on the left, downward and to the right. Its lowest border was 3.5 cm. below, and 1.5 cm. to the right of the umbilicus. A deep notch could be felt on its

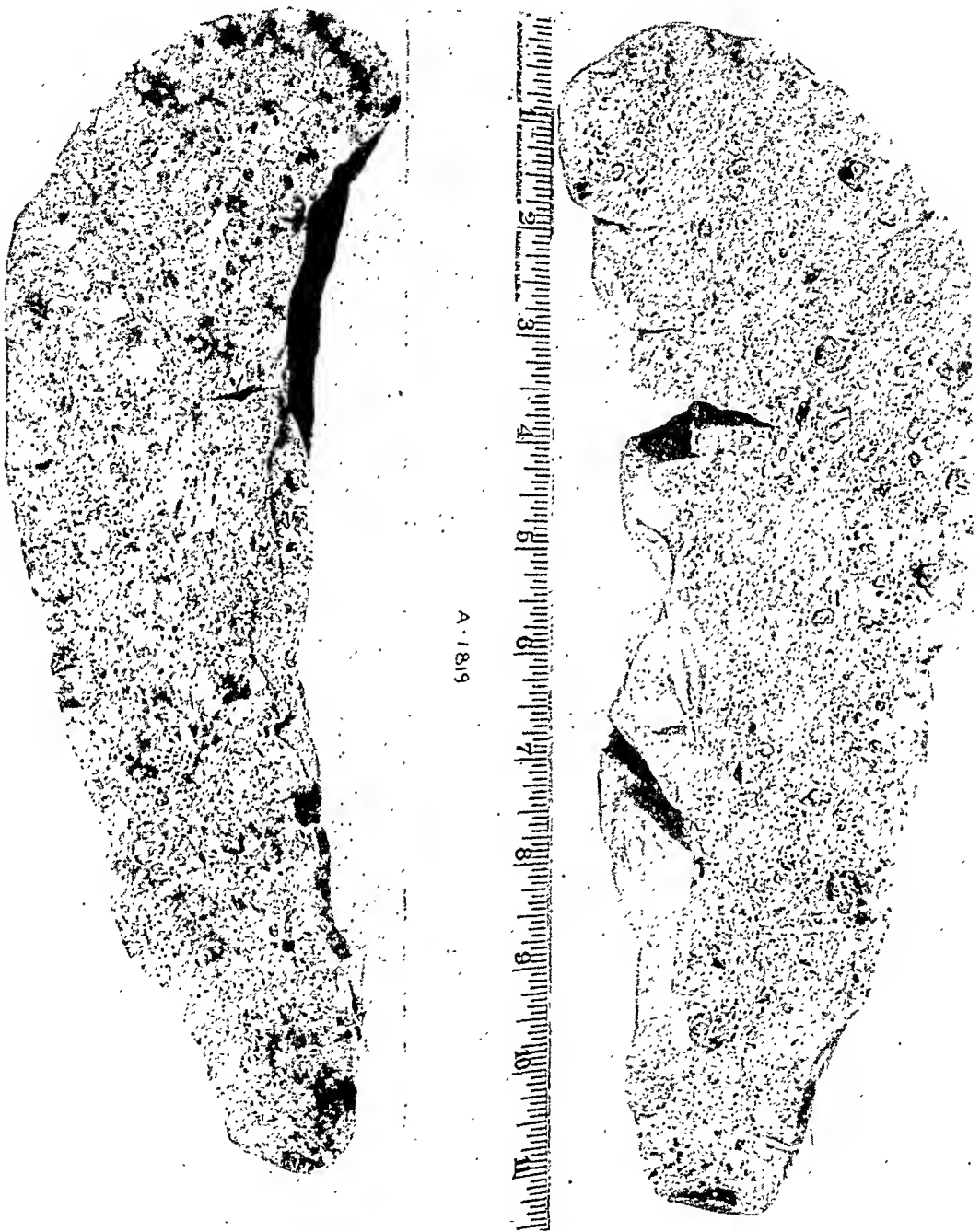


FIG. 4. Spleen—sectioned.

right border. It was freely movable but did not move with respirations. A roentgen-ray after pneumo-peritoneum-revealed a very striking picture of this mass which was believed to be the spleen.

In addition there was a marked clubbing of the fingers but otherwise the physical and neurological examinations were not remarkable. The pulse rate, temperature and respirations were normal.

A considerable amount of laboratory work was done, including numerous blood counts, platelet counts, blood chemistry determinations, renal function tests, liver function tests, fragility test, and gastric analysis. All these were normal. The sputum persistently showed gross and microscopic blood, but repeated examinations revealed no fungi, spirochetes or tubercle bacilli. The Wassermann reaction of the blood was four plus; that of his spinal fluid was negative.

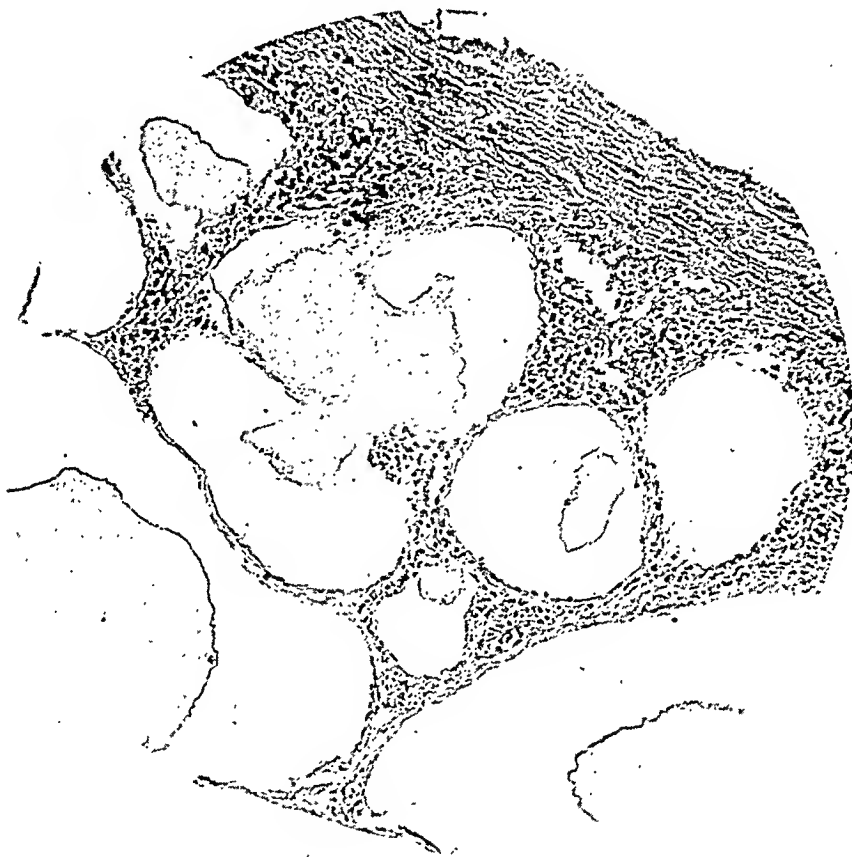


FIG. 5. Microphotograph of spleen (high power).

One month after his admission, the patient was examined bronchoscopically. This procedure was attended by considerable bleeding, and shortly thereafter he developed what was obviously a lung abscess. During a violent coughing attack two months later, he died. During his stay in the hospital, stringent anti-syphilitic treatment had been given.

The clinical diagnosis was (1) syphilis of the lung, (2) amyloidosis or multiple gummata of the spleen, and (3) lung abscess. An autopsy was performed three hours after his death and the complete protocol is appended herewith.

The body was that of a fairly well developed, poorly nourished white male in early middle life. The skin showed no striking abnormalities anywhere. The pupils were round and equal, and moderately contracted. The nasal septum was intact. The buccal mucous membranes and the teeth were not remarkable. The genitalia were

normal. There was marked clubbing of the fingers and loss of the nail on the right forefinger.

The body was opened in the usual manner, and considerable subcutaneous emphysema was noted. The peritoneal surfaces were smooth and glistening. The spleen, which will be described in detail later, extended beyond the midline to the right side, diagonally across the abdominal cavity, so that it terminated about 4 cm. to the right and 4 cm. below the umbilicus. The liver was about three fingers-breadth below the



FIG. 6. Cross specimen of lung (sectioned). Note: left lung is entirely normal.

costal margin. Otherwise the arrangement and color of the organs appeared normal. The left pleural cavity presented no adhesions and contained no fluid. The right pleural cavity, however, was abnormal. The pleural surfaces were in places bound down together. The lung was removed together with the pleural cavity by stripping the parietal pleura from the chest wall. About a liter of pus was removed from the anterior portion of this pleural cavity. Laterally and posteriorly the pleural surfaces were firmly bound down together, thereby obliterating completely the pleural space.

The pericardial cavity was everywhere smooth and glistening. There were no pericardial adhesions and no excess of fluid.

The heart weighed 300 gm. The valve measurements were: tricuspid, 12.5 cm., pulmonic, 7.5 cm., mitral, 8.5 cm., and aortic, 6 cm.

The heart was essentially of normal size. The epicardial surface was, in places, somewhat thickened. It had a dull grayish appearance, but there was no exudate. There was no atrophic change in the sub-epicardial fat and the surface vessels were not tortuous. The myocardium was not remarkable. When first sectioned there were some areas that looked like fresh scarring, but these were not evident later. The endocardium was normal. The mitral valve was entirely normal. The aortic valve re-

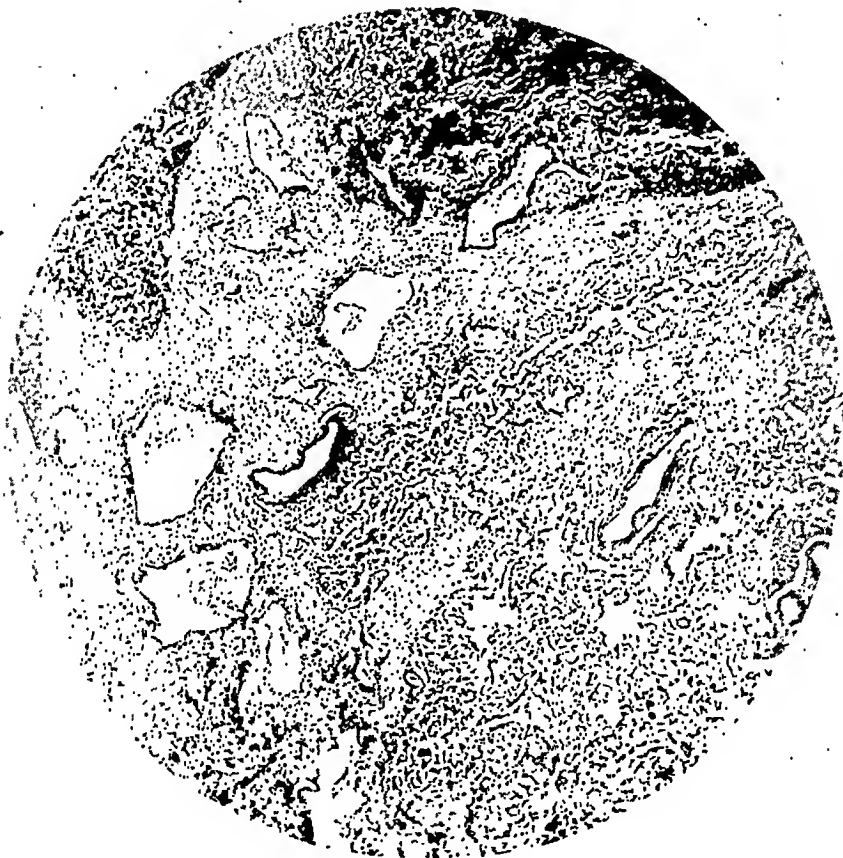


FIG. 7. Microphotograph of right lung.

vealed a few fenestrations but it was otherwise smooth and delicate. The tricuspid and pulmonic valves were normal. The openings of the coronary arteries were patent and the arteries themselves were smooth and delicate. In the pulmonary artery and just above the anterior leaflet of the pulmonic valve there was a small cyst. This was perfectly clear and measured about 1 mm. in diameter.

The pleural surface of the *left lung* was perfectly smooth and delicate, and on section the lung was entirely normal. There were no areas of consolidation and no cysts were seen in this lung. However, one of the bronchial nodes on this side contained calcified tubercles and another one just above it was entirely cystic and contained a clear greenish yellow fluid.

The *right lung*, however, was strikingly abnormal. It was moderately increased in size and the visceral and parietal pleurae were bound together posteriorly. Anteriorly was the empyema cavity, previously described. On cut section between the visceral and parietal pleurae, were a large number of multilocular cysts. These measured between 1 mm. and 1 cm. in diameter; some were hemorrhagic, while others contained a greenish yellow coagulated substance. The upper lobe of this lung was air-containing and apparently of normal color. The lower lobe was unusual. Posteriorly, extending from the bronchus, a small abscess cavity was seen. It was lined with exudate and from it, extending anteriorly and piercing both visceral and parietal pleurae, extended an opening somewhat less than 1 cm. in diameter. That this must

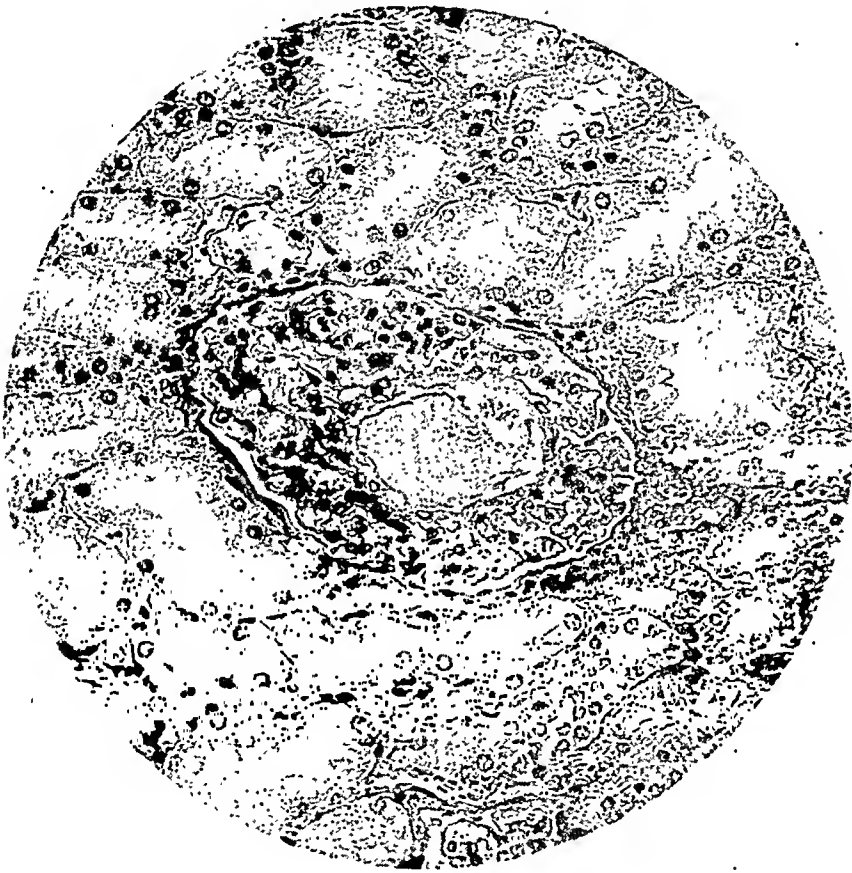


FIG. 8. Microphotograph of kidney showing a cyst in one of the glomeruli. This contains clear colloid.

have existed in this fashion for some time was obvious, because both layers of pleurae were fused together about this opening and the entire tract that had been so produced was lined with a shaggy exudate.

Anteriorly, in the lower lobe, were the following changes. Along the mediastinal border there was a round lobulated mass which measured 4 cm. across its greatest diameter. On section this contained within it many yellowish caseous looking necrotic areas, and extending into it from the outside were bands of scar tissue. This area was extremely vascular. By another section made 2 cm. posteriorly this cavity was reduced to a diameter of 2 cm. Beyond this were seen many cysts, most of which were near or around the blood vessels. The smallest measured about 1 or 2 mm. in

diameter, while the largest one within the lung measured 1.5 cm. in diameter. Most of them were blood tinged; many contain organized thrombi, while a few contained a perfectly clear, yellow, mucoid appearing, coagulated material. The entire lower lobe contained a brownish golden pigment quite like hemosiderin, and no such pigment was seen at all in the upper lobe. About the hilus of the lung and diminishing toward the parenchyma was a considerable amount of scar tissue. In the interlobar septum between the upper and lower lobes, two large cysts were observed. Practically every bronchial and mediastinal lymph node was involved in the same cystic degeneration and all contained the material just described, with the exception of two which, in addition, contained some yellowish caseous or necrotic-looking material. The middle lobe could not be found in this lung.

The *liver* weighed 2 kg. and measured 25 by 19 by 9 cm. It appeared moderately increased in size. The capsule was smooth and delicate, but beneath it, particularly over the right lobe, were myriads of angiomata which varied from pin point to 3 mm. in size. On the cut surface only one such nodule was seen within the depth of the liver itself. There was in places a suggestion of increase in fibrous tissue, but on the whole the liver appeared quite normal.

The *spleen* weighed 2100 gm. and measured 31 by 21 by 10 cm. Its enlargement was remarkable. Externally, the capsule was not increased in thickness and there was only one adhesion between the spleen and the lateral abdominal wall. The surface was roughened and myriads of cysts could be seen peering through it. On cut section there was nothing to be recognized as normal spleen. The entire organ was a cystic mass which simulated closely the above described changes in the lung—namely cysts (a) containing greenish yellow, clear, coagulated fluid. (b) Those containing organized thrombi. (c) Many blood tinged. (d) An occasional one containing necrotic or caseous looking material. These cysts were separated one from the other by a dense grayish yellow fibrous tissue stroma. Only a few blood vessels could be identified as such and their walls were moderately thickened. On cut section the surface suggested a slab of granite marble.

The *pancreas* was not remarkable. The peripancreatic lymph nodes are involved in the same general process.

The *kidneys* were of normal size. The capsules stripped easily. On the surface of both kidneys, however, many small hemangiomata similar to those described on the surface of the liver were seen. On cut surface the right kidney had a peculiar mottled appearance. However, the cortex was everywhere of normal width, and the striations were entirely regular. The pelves were not dilated. The ureters were normal. The bladder was normal. The right kidney weighed 200 gm. and measured 12.5 by 7 by 3 cm. The left kidney weighed 220 gm. and measured 14 by 7 by 3 cm.

The *pre-aortic* and *mesenteric lymph nodes* were likewise involved in the same cystic process. Nothing abnormal was noted in the *stomach*, *gastrointestinal tract*, *prostate gland*, *seminal vesicles*, or *aorta*.

On microscopic examination the *heart* seemed entirely normal and in two sections there was no evidence of any pathological change. The myocardium presented no scarring as mentioned above. The capsule of the *liver* was normal, and most of the liver cells appeared in a good state of preservation. There were no areas of necrosis and there was no amyloid. Many cysts were seen in these sections. Some of them were perfectly clear. Several contained fresh blood and one in particular contained both blood and a clear colloidal substance which stained pink and was probably serum. Most of these cysts appeared along the periphery of the organ and just under or in continuation with the capsule. A few, however, were seen deeper in the liver substance. These cysts in their proliferation seem to have followed several of the portal spaces. They were usually round or oval and many showed a definite endothelial lining. About several of them a moderate lymphocytic reaction could be seen.

The *spleen* was not recognizable as such. No Malpighian bodies could be seen, and the normal splenic pulp was completely replaced. One saw only myriads of cysts shrouded in a dense connective tissue stroma which had some lymphocytes scattered throughout. The endothelial lining could be seen in most of these cysts, and the vast majority contained colloid. Some contained fresh blood and in at least one an organized thrombus was found. In places, it seemed as if the fibrous tissue trabeculae of the stroma were extending into the cysts themselves.

In the *kidney*, most of the glomerular and tubular tissue appeared normal. However, many cysts were found in this organ as well. These were essentially of the same type as described but were found within the glomeruli themselves. Most of them were filled with colloid and red blood cells and under high power were seen to have an endothelial lining made up of only two or three cells, but even in this minute state some seem to be multilocular. Other large cysts or hemangiomas were found in the interstitial tissue between the tubules and approached the size of those seen in the liver.

The *adrenals* were essentially normal except that in a single section two cysts were found.

The *pancreas* was normal except for a few microscopic, colloid-bearing cysts.

One section of a *lymph node* revealed the replacement of the normal tissue by this cystic process.

The *left lung* was entirely normal. Many sections were taken from the *right lung* and the first studied was from the portion near the hilus where a considerable amount of dense scar tissue was seen grossly. This was borne out microscopically and within this dense scar tissue, many small cysts, some filled with blood, were seen. This was the area which corresponds to the mass seen by roentgen-ray in 1927, and the thick walls about the cysts in this area suggested that the process may have dated back to that time. The remainder of the section showed many small cysts and in addition necrotic abscess cavities undergoing liquefaction. There were many leukocytes in these cavities and polymorphonuclear cells predominated. About each of the smaller blood vessels, both in the scar tissue and the remainder of the lung spaces, a very striking ring of what seems to be elastic tissue could be seen, and that this was really elastic tissue was borne out by a Verhoeff-Van-Gieson stain. One also saw many large phagocytic cells containing considerable blood pigment. The alveoli that remain are large, emphysematous in type, and with thinned-out friable walls. A stain for tubercle bacilli was entirely negative.

A second section was taken from the area described as spherical and containing caseous or necrotic areas. Microscopical examination revealed these to be small abscess cavities probably pyogenic in origin since most of the reaction was of the polymorphonuclear type. There was no well defined capsule about these abscesses and many of them were undergoing liquefaction in their centers. The spaces between these abscesses were filled with scar tissue and the vessels in this tissue also showed, though in lesser degree, a rim of elastic tissue. Such elastic tissue was found only about the smaller vessels and never about the cysts. Many small cysts were also seen in this section, and toward the periphery, larger and more typical hemangiomas were found. These larger cysts were all very well defined and each showed a definite lining of endothelial cells. In one area there was definite bone formation with marrow within it. Another area likewise showed bone formation but no marrow was observed. The position of this bone formation was peribronchial and it was considered to be an example of metaplasia. The bronchi in this section were full of exudate which was similar to that in the abscess cavities. A search for acid-fast bacilli revealed none. A third section from the base added nothing that has not been described previously.

A fourth section was taken from the periphery of the lower lobe in the mid-

portion at the axilla. From without inward it was seen that the parietal pleura and visceral pleura were both thickened and contained considerable granulation tissue which showed new sprouting capillaries throughout. These are extremely numerous and pervade the entire substance. Between these layers, one saw many cysts filled with colloid and lined with endothelium. Several cysts also contained blood, but none was found which contained thrombi.

The fifth section was taken from the trachea and included a peritracheal lymph node of the mediastinal group. It showed normal lymphoid tissue to have been completely replaced by cysts.

Anatomical Diagnosis. Histologically benign, metastasizing hemangiomata involving spleen, liver, kidneys, pancreas, adrenals, intima of the pulmonary artery, the right lung, the mesenteric, peripancreatic, pre-aortic and mediastinal lymph nodes. Pyogenic abscess in the lower lobe of the right lung, with a bronchopleural fistula, pyothorax and subcutaneous emphysema; moderate cardiac hypertrophy.

This unusual condition, clinically so misjudged because of the positive Wassermann reaction, was, at postmortem examination, accompanied by no evidence of syphilis. Other cases similar to ours have been reported in the literature since 1879 (Langhans) but in no instance have we been able to find another case in which a positive Wassermann reaction was present. It seems clear that there is no connection between these two conditions. The name, histologically non-malignant metastasizing hemangioma, was first used by Thomas Shennan in his report of a case. Other authors have called this condition "telangiectatic splenomegaly," "diffuse hemangioma," "malignant hemangioma," "obliterating angioma," etc.

Most of the reported cases do not show the widespread involvement observed in ours. On the other hand a few have revealed foci that were not involved in this case. In Shennan's case the spleen weighed 1510 gm. and there were cystic spaces in the sternum and clavicle. In Homans' case the omentum was involved. Theile reported cystic changes in the stomach.

In addition to these, many pathologically similar examples in which only the spleen is involved can be found in the literature. However, we do not believe that in any case thus far described have the changes been so widely diffused as in this one.

BIBLIOGRAPHY

1. ALBRECHT, H.: Ueber das Cavernom der Milz. Ein Beitrag zur Kenntnis von Bau und Entstehung der Cavernome, Ztschr. f. Heilk., 1902, xxiii, 97.
2. ANZILOTTI, G.: Sugli angiomi multipli della milza, Tumori, Roma, 1913-14, iii, 261.
3. BENCKENDORFF, ELISABETH V.: Untersuchungen eines Angiomes der Milz, Virchow's Arch. f. path. Anat., 1908, cxciv, 500.
4. BORRMANN, ROBERT: Zum Wachsthum und zur Nomenclatur der Blutgefäßgeschwülste, Virchow's Arch. f. path. Anat., 1899, clvii, 297.
5. HOMANS, JOHN: Report of a case of cavernous angioma of the spleen, Ann. Surg., 1897, xxv, 732.
6. LANGHANS, THEODOR: Casuistische Beiträge zur Lehre von den Gefäßgeschwülsten, Virchow's Arch. f. path. Anat., 1879, lxxv, 273.
7. THEILE, DR. MED.: Über Angiome und sarkomatöse Angiome der Milz, 1904, clxxviii, 296.
8. DOWN, C. N.: Cavernous angioma of the spleen, Ann. Surg., 1915, lxii, 177.

9. SYMMERS, DOUGLAS: Telangiectatic splenomegaly, Jr. Am. Med. Assoc., 1921, lxxvii, 2019.
10. WRIGHT, A. W.: Primary malignant hemangioma of the spleen with multiple liver metastases, Am. Jr. Path., 1928, iv, 507.
11. KELLERT, ELLIS: Diffuse hemangioma of the spleen, Am. Jr. Cancer, 1932, xvi, 412.
12. SHENNAN, THEODORE: Histologically non-malignant angioma, with numerous metastases, Jr. Path. and Bact., 1914-15, xix, 139.
13. STEINER, W. R.: Hereditary hemorrhagic telangiectasia, Nelson Loose Leaf Medicine, Volume IV (Diseases of blood, circulatory system, kidney), 162A.
14. WOLLSTEIN, MARTHA: Malignant hemangioma of the lung with multiple visceral foci. Report of a case, Arch. Path., 1931, xii, 562.

INFECTIOUS MONONUCLEOSIS COMPLICATING TYPHOID FEVER *

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THE simultaneous occurrence of typhoid fever and infectious mononucleosis has not previously been recorded in the literature. The case reported below is an instance of such coincidence.

CASE REPORT

Dr. I. S., aged 25, a member of the house staff of this hospital, was admitted to the service of Dr. Charles R. Austrian on August 29, 1937, complaining of malaise and sore throat of three days' duration. Except for a history of asthma in the father and hay fever in one brother, the family history was negative. The patient had the usual diseases of childhood without sequelae and a tonsillectomy at the age of six. At 10 he had diphtheria and was treated with antitoxin. He had also had recurrent luxation of the right humerus and a right eustachian salpingitis for the previous five years. One year before admission, he had received only two of the recommended three injections of typhoid-paratyphoid combined vaccine (0.5 c.c. and 1.0 c.c., at an interval of one week).

Three days before admission the patient noted that his throat felt a little sore, but continued with his work. He suffered so little discomfort that the afternoon before admission he went swimming. A few hours later, he noticed a recurrence of his sore throat and felt alternately feverish and chilly. His temperature at this time was 101.5° F. Because of increasing malaise, the patient was admitted to the hospital on the following morning.

On admission, the temperature was 100° F., pulse 88, respirations 16. The patient was a tall, asthenic young man, somewhat underweight, who appeared to be moderately ill. The skin was warm and dry; there was no exanthem. No general or localized glandular enlargement was noted. The pupils were round, regular, equal, and reacted briskly to light and accommodation. There was no nasal discharge or inflammation of the nasal mucous membrane and although the pharynx and fauces showed a diffuse reddening, there was no exudate. Small tonsillar tags were seen. The thyroid gland was not enlarged. The lungs were clear except for a few transient sibilant rhonchi, and the heart was negative. The genitalia and extremities were nor-

* Received for publication May 18, 1938.

From the Department of Medicine, Sinai Hospital of Baltimore.

mal. The neurological examination revealed no abnormalities. The number of leukocytes on admission and subsequently are recorded in table 1. There was no anemia. Urinalysis was negative. The Wassermann reaction of the blood serum was negative. Throat cultures revealed a mixed growth of pneumococcus, staphylococcus, *Micrococcus catarrhalis*, and non-hemolytic streptococcus. No Klebs-Loeffler or Vincent's organisms could be demonstrated.

The temperature was remittent with a morning fall to around 100° F., and a rise to levels between 102° and 104.6° F. at night. The pulse rate ranged between 88-100 a minute during the febrile period. The posterior cervical lymph nodes became slightly enlarged shortly after admission. On September 1, the third day after admission and the seventh day after the onset, *Bacillus typhosus* was identified in culture from the blood and the same organism grew in numerous subsequent cultures of the urine and stools. Early in the course of the disease, the patient's chief complaints were nausea, anorexia, chilly sensations, and generalized malaise. A week after admission, he complained of an intensely severe sore throat which was much more pain-

TABLE I
Leukocyte Counts

Date	W.B.C. per cu. mm.	Juv. PMN %	PMN %	Lymph. %	Mono. %
8-29-37	5850	9	61	25	5
8-30-37	3300	30	42	23	5
8-30-37	3750	27	31	40	2
8-31-37	5000	34	19	37	10
9-1-37	4000	22	20	54	4
9-2-37	5350	13	32	52	3
9-3-37	5950	17	27	54	2
9-4-37	7900	16	20	64	0
9-5-37	8200	13	17	69	1
9-6-37	7400	14	12	74	0
9-7-37	16500	10	14	72	4
9-8-37	12700	14	12	67	7
9-9-37	10400	12	21	63	4
9-10-37	10750	14	25	51	10
9-11-37	10400	0	32	41	27
9-12-37	8550	6	24	57	13
9-15-37	6200	7	29	55	9
9-24-37	6050	0	33	62	5
9-29-37	5800	7	56	31	6

ful than the initial mild irritation. For the next 10 days, faucial pain was constant and severe. The mucous membrane of the fauces and pharynx continued to show a diffuse, dusky erythema, but no exudate developed. During this period a shallow ulcer, about 1 cm. in diameter, developed at the base of the right tonsillar fossa and although it persisted for two weeks in spite of local treatment, it did not increase in size. Repeated cultures of the oral cavity revealed no change in the flora. At the onset of this sore throat, the moderately firm, rounded edge of the spleen became palpable just below the costal margin, but there was no general enlargement of the peripheral lymph nodes at this or any other time during the course of the illness. There was no change in the size of the posterior cervical nodes. The tonsillar glands were a little enlarged and moderately tender.

Because of the severity of the pharyngeal manifestations, and because of the increasing leukocytosis with a marked preponderance of mononuclear elements, it was thought that infectious mononucleosis had developed. On September 9, a heterophile

antibody agglutination was positive in a dilution of 1:256 (table 2). On the following day, the monocytes of the blood rose to 10 per cent of the total white cell count, and two days later they constituted 27 per cent of the leukocytes (table 1). The temperature did not rise above normal limits on September 12, and from this time on the patient improved rapidly without further complications. Repeated cultures of the urine and stools were negative for *Bacillus typhosus* after the defervescence, and the patient was discharged cured on October 1.

TABLE II
Agglutination Reactions

Date	Agglutination Titer				
	9-1-37	9-5-37	9-9-37	9-15-37	10-15-37
Antigen					
<i>B. typhosus</i>	1 : 50	1 : 160	1 : 320	Not done	Not done
<i>B. paratyphosus A.</i>	0	1 : 20	1 : 160	Not done	Not done
<i>B. paratyphosus B.</i>	1 : 50	1 : 40	1 : 160	Not done	Not done
<i>B. suipestifer</i>	Not done	1 : 20	0	Not done	Not done
<i>B. dysentery</i> (polyvalent) ..	Not done	1 : 20	0	Not done	Not done
<i>B. proteus</i> X2 and X19	Not done	0	0	Not done	Not done
<i>B. melitensis</i> —bovine	Not done	0	0	Not done	Not done
porcine	Not done	0	0	Not done	Not done
caprine	Not done	0	0	Not done	Not done
Sheep cells	Not done	Not done	1 : 256	1 : 128	1 : 64

COMMENT

The diagnostic problem of differentiating between typhoid fever and infectious mononucleosis arises not infrequently. Malaise, headache, epistaxis, slight sore throat, fever and relative bradycardia are early manifestations encountered commonly in both diseases. It is of interest that both these diagnoses were suggested early in the course of this case. The demonstration of *Bacillus typhosus* in cultures of the blood, of the urine, and of the stools and the increasing titer of the Widal reaction established the diagnosis of typhoid fever.

Suspicion that an unusual complication might be present was aroused because of the prominence of the pharyngeal manifestations associated with the sudden rise of the leukocytes to 16,500 per cu. mm., 76 per cent of which were mononuclear cells. In his analysis of 829 cases of typhoid fever treated at the Johns Hopkins Hospital during the first 10 years of its existence, Osler³ found only five cases in which the pharyngitis was sufficiently severe to cause annoyance and require local treatment. In Thayer's² investigations of the blood counts found in this same series, there is no record in which the percentage of polymorphonuclear cells fell to such low levels in the presence of so marked a leukocytosis. The demonstration in the patient's blood serum of agglutinins for sheep cells in a dilution of 1:256 in the absence of any recent administration of horse serum, indicated clearly that infectious mononucleosis complicated the primary disease. Although Bernstein¹ demonstrated the presence of bacterial agglutinins in a number of cases of infectious mononucleosis, he found no increase of the agglutinins for sheep erythrocytes in the serum of a series of pa-

tients with typhoid fever. The subsequent appearance of an increase in the number of atypical monocytes to 27 per cent of the total leukocyte count, confirmed the clinical and serological findings.

Although it is obvious that the two injections of combined typhoid-paratyphoid vaccine administered in 1936 failed to immunize the patient adequately, it may be that the severity of the typhoid infection was ameliorated thereby, as the febrile period lasted only 17 days despite the presence of an unusual complication.

SUMMARY

A case of typhoid fever complicated by infectious mononucleosis is presented.

REFERENCES

1. BERNSTEIN, A.: Antibody responses in infectious mononucleosis, Jr. Clin. Invest., 1934, xiii, 419.
2. THAYER, W. S.: Studies in typhoid fever, 1901, The Johns Hopkins Press, Baltimore, iii, 489.
3. OSLER, W.: *ibid.*, iii, 457.

EDITORIAL

OBSCURE FORMS OF SUBACUTE COR PULMONALE

During recent years in which clinicians in the United States have become interested in the syndrome of right heart failure, the causes of increased resistance to the pulmonary circulation have been restudied. The problem is a fascinating one because we possess as yet no direct method of measuring the pressures in the pulmonic arteries or veins and must proceed largely through indirect means.

Our basic information we owe to the postmortem observations of disproportionate hypertrophy and dilatation of the right ventricle in certain lesions of the lungs which would apparently entail a diminution in the pulmonary vascular bed; for example, in extensive pulmonary fibrotic processes, in extreme kypho-scoliosis with disproportionately small lungs, in massive types of silicosis, and occasionally in high grades of emphysema. It has become evident in the study of such pulmonary lesions that it is only diffuse lesions which can cut down the cross section of the pulmonary blood flow sufficiently to cause a heightened resistance to the normal output of the right ventricle. We know, for instance, that total collapse of one lung or, indeed, the removal of one lung can be compensated by the full utilization of the vascular bed of the remaining lung without apparent strain upon the right heart.

Such diffuse pulmonary lesions as have been mentioned are usually detectable by clinical methods of examination. The development of right heart failure in these may often be followed from the early stage in which it is doubtful whether the dyspnea present is chiefly pulmonary or chiefly circulatory to the time when engorged jugulars, enlarged liver and edema of dependent parts indicate plainly the congestion secondary to failure of the right ventricle.

Far less easy to interpret clinically are certain cases of dyspnea and cyanosis of subacute type, apparently of circulatory origin, in which the only abnormalities discoverable by physical examination, roentgenography and electrocardiography are evidences of dilatation of the pulmonary conus and main pulmonary arteries, accentuated second pulmonic sound, and right axis deviation. These indicate pulmonary arterial hypertension and right ventricular hypertrophy, but the nature of the increased resistance in the pulmonary circuit remains unrevealed.

There are at least three conditions which may give rise to such a clinical picture: (1) primary pulmonary arteriosclerosis; (2) pulmonary arteritis; and (3) lymphangitic carcinomatosis of the lungs.

If the strict criteria set up by Steinberg are followed, the condition known as primary pulmonary arteriosclerosis is a very rare one. Steinberg advised the restriction of the term to those cases in which there was absence of all

lesions known to produce pulmonary arteriosclerosis as a secondary consequence. This would exclude cases showing mitral stenosis, congenital cardiac and vascular anomalies with communication between the systemic and pulmonic circulations, congenital narrowing of the pulmonary veins, outspoken emphysema, diffuse pulmonary fibroses and extensive pleural adhesions. In addition, it should be noted that Brenner¹ has shown that moderate grades of pulmonary arteriosclerosis are very frequently found without any evidence at autopsy of right ventricular hypertrophy or clinical history suggesting right heart failure. There remain, however, instances in which right heart failure was present in life without obvious explanation, and in which careful postmortem studies disclosed as the sole apparent cause extensive sclerosis in the small arteries and arterioles of the lungs. The microscopic details of the arterial lesions are in no way specific. In certain reported cases marked intimal proliferation had led to partial or complete occlusion of the vessels, while in other cases the media was more prominently involved. In one of Brenner's cases with marked hypertrophy and dilatation of the right heart no pathogenic factor other than the pulmonary arteriosclerosis was found, but the extent of the arterial change present seemed no greater than this author had observed in other cases presenting no evidence of right heart strain. It has been suggested that such cases are explainable by the occasional occurrence of an essential pulmonary hypertension due to vasoconstriction, analogous to essential hypertension in the systemic circulation, and that the changes in the smaller pulmonary vessels and in the right ventricle occur only as a secondary effect. Direct evidence for the validity of such a conception is lacking.

In certain instances the clinical picture of subacute or chronic right heart failure may develop as a result of diffuse arteritis or thromboarteritis of the pulmonary arteries. In the majority of cases of arteritis, however, whether or not associated with thrombosis, clinical and pathological evidences do not indicate that pulmonary hypertension had existed in life.²

A specific form of arteritis due to syphilis, and accompanied by chronic right heart failure, polycythemia and marked cyanosis, has been described by several authors and is usually given the name of Ayerza's disease. The reported cases have been reviewed by Brenner who concludes that the proof of the syphilitic nature of the arterial lesions is in almost all of these cases quite unconvincing. Syphilis of the pulmonary aorta and large pulmonary arteries has been established in a number of cases,³ most of which, however, presented no evidence of pulmonary hypertension. It seems probable that syphilis of the small arteries and arterioles with consequent right heart over-

¹ BRENNER, O.: Pathology of the vessels of the pulmonary circulation. Part IV, Arch. Int. Med., 1935, lvi, 976.

² BRENNER, O.: Pathology of the vessels of the pulmonary circulation. Part V, Arch. Int. Med., 1935, lvi, 1189.

³ KARSNER, HOWARD T.: Sclerosis of the pulmonary arteries, Chapter XVI in "Arteriosclerosis" (edited by EDMUND V. COWDRY, PH.D.), 1933, The Macmillan Company, New York, p. 457.

load is extremely rare, and that many of the cases in which it was suspected are examples of primary or secondary pulmonary arteriosclerosis.

Rheumatic pulmonary arteritis, diffusely involving the arterial tree in the lungs, has been accepted as an entity, but data are not available as to the effect on the pressure in the pulmonary arterial circulation.

In septic states minor embolisms of the lesser branches of the pulmonary arteries are probably far more frequent than is commonly realized. Under certain conditions such emboli become organized with partial or complete occlusion of pulmonary vessels. Occasionally secondary arteritis with propagating thrombi may occur. There are also non-embolic forms of pulmonary arteritis occurring in septic states, and over such areas of arteritis occluding thrombi may form.⁴ Occasionally in this whole group of cases, an instance is observed in which the typical picture of right heart failure has supervened.

The third category of cases mentioned included those in which pulmonary hypertension resulted from lymphangitic carcinomatosis of the lungs.⁵ Clinically these cases are only rarely diagnosed, since they tend to occur before the usual age for carcinoma, and the primary growth which is usually in the stomach has a striking tendency to be symptomatically latent. In the forefront of the clinical picture stands an unexplained increasing dyspnea with evidences of right heart strain. The pulmonary physical signs are slight or absent, and no gross changes in the lungs are found in the roentgenogram. A fine reticular pattern in the lung parenchyma has been described as a helpful sign. The course is rapidly downhill with increasing tachypnea and asphyxial episodes.

Autopsy reveals the primary tumor which is often a flat diffusely infiltrating scirrhous gastric carcinoma, but may be situated in other organs. The gross appearance of the lungs may be normal, but often the subpleural lymphatics show as a white network. Microscopically the perivascular and peribronchial lymphatics are distended with tumor cells. In addition, the lesser arteries are frequently plugged with tumor thrombi in various stages of organization. The smaller arteries show a widespread sclerosis with partial or complete obliteration of their lumens. It is assumed that this latter change is due to a toxic effect of the adjacent tumor growth in the perivascular lymphatics. The right ventricle is usually dilated and may also show marked muscular hypertrophy of its wall. While the mechanism of this type of tumor dissemination is still far from clear, the condition itself is a relatively well defined entity and should be remembered in the study of any case of obscure dyspnea with unexplained right heart failure.

M. C. P.

⁴ FOWLER, W. M.: Obliterating thrombosis of the pulmonary arteries, *ANN. INT. MED.*, 1934, vii, 1101.

⁵ JARCHO, SAUL: Diffusely infiltrative carcinoma. A hitherto undescribed correlation of several varieties of tumor metastasis, *Arch. Path.*, 1936, xxii, 674.

REVIEWS

Diagnosis and Management of Diseases of the Biliary Tract. By R. FRANKLIN CARTER, M.D., F.A.C.S.; CARL H. GREENE, PH.D., M.D., F.A.C.P.; JOHN RUSSELL TWISS, M.D., F.A.C.P. 432 pages; 24 × 15.5 cm. Lea and Febiger, Philadelphia. 1939. Price, \$6.50.

The authors have written an interesting book based in large part upon the data accumulated during the past 20 years in the special clinic for diseases of the liver and biliary passages which is a part of the New York Post-Graduate Medical School and Hospital. The relatively uniform use over considerable periods of a routine of investigation and of management of cases falling in this group adds to the value of such data. The authors, as a result of their study, have arrived at a definite point of view concerning many controversial topics.

There is an adequate discussion of the difficult subject of biliary dyskinesia and deductions are drawn as to the proper clinical management in individual instances. Other chapters contain procedures for duodenal drainage, hepatic function tests and biochemical methods of investigation. The entire subject of gall-bladder infection is fully dealt with both from the laboratory and clinical standpoints.

The whole latter section of the volume is devoted to the operative experiences of the clinic, and the conclusions derived seem to be in accord with the general trend of thought. There are added to nearly every chapter good bibliographies which add greatly to the value of the book.

The chief criticism is the large amount of repetition. In addition, some of the very recent contributions, such as the use of vitamin K in jaundice, are incompletely presented.

On the whole the subject is handled very well, and the volume is one that should be read by anyone interested in gastroenterology.

F. G. D.

The Physiology of Anesthesia. By HENRY K. BEECHER, A.B., A.M., M.D. 388 pages; 24 × 16 cm. Oxford University Press, New York City. 1938. Price, \$3.75.

The author has presented the physiology of the anesthetic drugs in a clear, concise way. The numerous theories of narcosis are given in detail. The general action of anesthetics, as well as their effects on various systems of the body, are dealt with. It is a treatise which will be read with profit both by anesthetists and by internists.

T. R. A.

Laboratory Manual of the Massachusetts General Hospital. By FRANCIS T. HUNTER, M.D. 119 pages; 18 × 12.5 cm. Lea and Febiger, Philadelphia. 1939. Price, \$1.75.

The author preserves in the revised edition the purpose and scope of the original manual. The book continues to be an excellent pocket reference for medical students, internes and practising physicians, containing only diagnostic and therapeutic procedures of proved value which have been systematically arranged and briefly written.

E. F. C.

Play Therapy in Childhood. By C. H. ROGERSON, M.D., M.R.C.P., D.P.M. 64 pages; 21.5 × 14 cm. Oxford University Press, New York City. 1939. Price, \$1.25.

This book is a short, very readable treatise on a recent and most promising technic in the psychiatric treatment of problem children. The author presents a study of 36

rather severe cases treated by this method. He describes four of these cases in some detail, and his general conclusions are based on the findings of the larger group. In the first chapter he gives the history of the development of this technic and discusses the literature. Throughout the book the author shows a sane, common sense approach to a topic that is confused by theoretical controversies. The book is indispensable to pediatricians who wish to study psychiatric and child guidance methods. It is also recommended to any physician who would appreciate a short, clearly written, well illustrated description of what takes place when a psychiatrist treats a problem child.

H. W. N.

Personality Development and Social Control in Terms of Constitution and Culture.
By IRA S. WILE, M.S., M.D. 57 pages; 21.5 × 14 cm. Oxford University Press, London. 1939. Price, \$1.25.

This little volume represents three lectures delivered at The Tavistock Clinic by Dr. Wile in July, 1937. The first, dealing with "Personality in Terms of Constitution," is a thoughtful consideration of the processes of structural change, which Dr. Wile winds up by saying: "If society is unable to make the needed adjustments in its external world, then the constitution is affected in a manner that stimulates it to attempt an adaptation of personality potentials to the demands of the situation." The second lecture is entitled "Personality in Relation to Culture." "It is obvious, therefore, that personality involves the mobilization of forces from within itself to meet specific cultural needs," including economics, personal rights and rights of others, sexual customs, religious and educational patterns. Of all this, Dr. Wile may be summarized in his own words: "Man is a microcosm in a macrocosm. He is an atom in a universe which exists only because there are atoms. But the relations of the atom are determined by the existence of the pressures of the universe. Man is thus a creator or a moulder of his world and at the same time a part of creation constantly moulded by the patterns in his multiple spheres of activity." The third lecture, "Social Control and the Prevention of Personality Disorders," is considerably longer than the other two. After recognizing the individual aspects, he goes into prevention of personality disorders as a social problem primarily referable to the community or to the nation. He reviews familiar facts of the economic waste of these illnesses, both in terms of the direct cost of the maintenance of the afflicted individual, and in terms of the frequently life-long drain upon the community's resources entailed by the loss of the services of these patients, many of whom are potentially fine minds, cut off in youth or early adult age. He makes some general suggestions as to social factors including various governmental security acts which may do something to contribute to the surety with which the individual develops.

H. M. M.

COLLEGE NEWS NOTES

A. C. P. COMMITTEES AND BOARD OF REGENTS TO MEET

The regular autumn meetings of the various special Committees of the College and of the Board of Regents will be held at the College Headquarters in Philadelphia, December 16-17. Matters for consideration and action include the review of the credentials of more than two hundred candidates for Associateship and Fellowship, the presentation of the program for the Twenty-fourth Annual Session to be held in Cleveland, April 1-5, 1940, the consideration of amendments to the Constitution and By-Laws, the presentation and adoption of a program of postgraduate courses for 1940, reports on future policies and many routine matters.

PROPOSAL OF CANDIDATES

Attention of Fellows is called to the provisions of the By-Laws whereby proposals of candidates must be filed in the Executive Office of the College, 4200 Pine Street, Philadelphia, at least thirty days in advance of action. Meetings of the Committee on Credentials are scheduled for the following dates:

December 16, 1939
February 25, 1940
March 31, 1940

GIFTS TO THE COLLEGE LIBRARY

An act of courtesy and thoughtfulness, the presentation of his autographed book to the American College of Physicians by one of its Fellows, was the inspiration for the founding of a library of books of which members of the College are the authors. The Library, in a sense, is a memorial library to our members. A general medical library, other than one of this character, would scarcely be justified at the College Headquarters due to the availability of so many general medical libraries in Philadelphia. However, the type of collection now well begun is quite different, and will have a growing interest, an increasing value and a deeper sentiment as the years pass by. Already several hundred books have been received; a considerable number of the authors, early members of the College, are now deceased, but these copies of their books remain, memorials to those men in the College Headquarters.

The following recent contributions are gratefully acknowledged:

Book

Dr. Robert T. Monroe (Associate), Boston, Mass.—“Chronic Arthritis.”

Reprints

Dr. Leila E. Andrews, F.A.C.P., Oklahoma City, Okla.—1 reprint;
Dr. Andrew L. Banyai (Associate), Wauwatosa, Wis.—20 reprints;
Dr. J. E. Greenstein, F.A.C.P., Providence, R. I.—1 reprint (in triplicate);
Dr. A. J. Logie (Associate), Jacksonville, Fla.—2 reprints;
Dr. Louis B. Owens (Associate), Cincinnati, Ohio—1 reprint;
Dr. Edw. C. Reifenstein, Jr. (Associate), Syracuse, N. Y.—11 reprints;

Dr. Ramon M. Suarez, F.A.C.P., San Juan, P. R.—2 reprints;
 Dr. August A. Werner, F.A.C.P., St. Louis, Mo.—2 reprints.

THE 1939 DIRECTORY OF THE COLLEGE

The new and revised Directory of the College has been completed and mailed to every member of the College in good standing in his dues. In addition, about two hundred copies were sent gratis to the leading medical schools, medical societies and medical institutions of the United States and Canada. The Directory has become widely used as an index to competent physicians both by members and these institutions. The Directory is never sold to commercial firms or for commercial purposes.

This Directory contains the names and biographical data of 4,204 physicians, including 1 Master, 2,969 Fellows and 1,234 Associates, comprising the full College Membership. The following analysis of the specialty listings of members reveals an increasing number of admissions to the College of doctors engaged in the allied and related specialties, such as neurology, psychiatry, pathology, pediatrics, radiology, student and public health, and dermatology and syphilology. It may be noted by the reader that there are a limited few who have indicated their primary interest in the surgical specialties, but it should be explained that these members are not new acquisitions but members of early standing in the College when the surgical specialties were not so strictly excluded, or men who in later years turned from their original medical specialties to surgical specialties.

SPECIALTY ANALYSIS OF THE 1939 DIRECTORY

	Primary Specialty	Secondary Specialty
INTERNAL MEDICINE.....	2740	34
Allergy.....	11	128
Arthritis.....	5	54
Aviation Medicine and Military Medicine... 8		15
Cardiology.....	54	547
Communicable Diseases.....	1	3
Diagnosis.....	3	20
Diseases of the Chest.....	48	174
Endocrinology.....	10	66
Gastro-enterology.....	40	256
Hematology and Blood Diseases.....		21
Immunology and Preventive Medicine..... 5		14
Medical Education and Administration..... 21		31
Metabolic Diseases.....	13	138
Nutrition.....		2
Parasitology.....		1
Physical Therapy.....		19
Research.....	2	56
Tropical Medicine.....	5	28
Tuberculosis.....	70	116
Total Sub-specialties.....	296	1689
TOTAL, INTERNAL MEDICINE.....	3036	1723
GENERAL MEDICINE.....	277	12
NEUROLOGY AND PSYCHIATRY.....	206	73
PATHOLOGY AND CLINICAL PATHOLOGY.....	169	120
PEDIATRICS.....	147	30
RADIOLOGY AND ROENTGENOLOGY.....	104	23
PUBLIC HEALTH, STUDENT HEALTH.....	58	29
DERMATOLOGY, SYPHILOLOGY.....	41	44
SURGICAL SPECIALTIES.....	12	9

MISCELLANEOUS

Anatomy.....	2	
Bacteriology.....	12	20
Biological Chemistry.....	2	2
Cancer.....	1	1
Industrial Medicine.....	11	11
Legal-Cultural Medicine.....		2
Life Insurance Medicine.....	2	1
Medical Editing.....	1	
Pharmacology.....	5	2
Physiology.....	7	1
Retired.....	111	
	<hr/>	
	154	40
No SECONDARY SPECIALTY GIVEN.....		2101
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	4204	4204

REGIONAL MEETING, NORTH CAROLINA

Under the Governorship of Dr. Charles Hartwell Cocke, Fellows and Associates of the College for the State of North Carolina held their regional meeting at the University of North Carolina, Chapel Hill, Friday, October 20, 1939. They were also invited to attend the Postgraduate Symposium on "Diseases of the Lungs and Thorax" at Duke University, Durham, October 19-21. Dr. W. C. Davison, Dean of the Duke University Medical School, was in charge of local arrangements. The program was as follows:

2:45 p.m. Opening.

Dr. Charles Hartwell Cocke, Asheville

3:00 p.m. An Unusual Type of Infection of the Lower Respiratory Tract in College Students.

Dr. W. Reece Berryhill, Chapel Hill

3:45 p.m. The Effect of Renal Injury upon the Regeneration of Plasma Proteins.

Dr. Russell L. Holman, Chapel Hill

4:30 p.m. Round Table Discussion—Diabetes.

Dr. T. Preston White, Charlotte

Dr. W. Raney Stanford, Durham

Dr. Paul F. Whitaker, Kinston

Dr. Roy C. Mitchell, Mt. Airy

6:30 p.m. Informal Supper.

Carolina Inn, Chapel Hill.

President O. H. Perry Pepper of the College was a guest at the meeting and spoke in the evening. Those who could remain were invited not only to attend the program at Duke University on Saturday, October 21, but were also invited to a barbecue lunch and thereafter to attend the Syracuse-Duke football game.

NEW YORK ACADEMY OF MEDICINE—FRIDAY AFTERNOON LECTURES

The New York Academy of Medicine recently announced its fourteenth series of Friday afternoon lectures for 1939-1940, to which the following Fellows of this College will contribute:

Dr. John Russell Twiss, F.A.C.P., Nov. 10, "Medical Management of Disorders of the Biliary Tract";

Dr. Richard A. Kern, F.A.C.P., Philadelphia, Dec. 1, "The Treatment of Visceral Allergies";

Dr. Alvan L. Barach, F.A.C.P., Dec. 15, "Recent Advances in Helium and Oxygen Therapy; Principles and Methods";

Dr. Yale Kneeland, Jr. (Associate), Jan. 5, "Primary Bronchopneumonia";

Dr. J. Burns Amberson, Jr., F.A.C.P., Jan. 26, "Choice of Treatment for Pulmonary Tuberculosis with Special Reference to Newer Surgical Procedures";

Dr. Soma Weiss, F.A.C.P., Boston, March 1, "Types of Syncope and Their Treatment";

Dr. Arthur C. DeGraff, F.A.C.P., March 29, "An Evaluation of Some of the Newer Drugs."

Dr. Francis M. Pottenger, F.A.C.P., Monrovia, Calif., a member of the first Board of Councilors of the American College of Physicians, and serving continuously in some official capacity for the College through 1939, was given a testimonial dinner by the Los Angeles Trudeau Society on the evening of September 26, a day preceding his seventieth birthday. Dr. Pottenger was instrumental in starting anti-tuberculosis work in Southern California with the founding of the Anti-Tuberculosis League, established in 1902, two years before the National Tuberculosis Association was founded. Dr. Pottenger was its first president and served until 1906. The Anti-Tuberculosis League was the ninth organization in the United States for the prevention of tuberculosis; eventually it was merged into the California Tuberculosis Association of which Dr. Pottenger served as president in 1931-32.

In accordance with a long standing custom, former patients of the Pottenger Sanatorium and Clinic, numbering nearly three hundred, gathered on the Sanatorium grounds for the Annual Home-Coming on October 1, further to honor Dr. Pottenger and to recognize his great service to them.

Under the Presidency of Dr. Rodney W. Bliss, F.A.C.P., the Omaha Mid-West Clinical Society held its Seventh Annual Assembly, October 23-27. Scientific exhibits were entered by:

Dr. Albert F. Tyler, F.A.C.P., "Technic of Electrocoagulation";

Drs. E. J. Kirk (Associate) and J. P. Tollman, "A Clinico-Pathological Study of Hypertension";

Drs. F. Lowell Dunn, F.A.C.P. and E. E. Simmons, "Fever Therapy in the Treatment of Rheumatic Fever."

Dr. Clifford J. Barborka, F.A.C.P., Chicago, presented a clinic on "Peptic Ulcer; Gall-Bladder; Obesity," acted as leader of a round table on "The Management of Colitis" and presented two formal papers, "Sub-Clinical States of Nutritional Deficiencies" and "Medical Management of Gall Bladder Disease."

Dr. William R. Houston, F.A.C.P., Austin, Tex., presented a paper on "Learned Reactions." Dr. Samuel A. Levine, F.A.C.P., Boston, gave a clinic on "Organic Heart Disease," led a round table on "Emergency Treatment in Acute Cardio-Vascular Diseases," and delivered two formal papers, "Bedside Diagnosis of Cardiac Arrhythmias" and "Rheumatic Heart Disease."

Dr. J. D. McCarthy, F.A.C.P., acted as Secretary and Director of Clinics. A considerable number of Fellows and Associates of the College from Omaha gave clinics.

Dr. August A. Werner, F.A.C.P., St. Louis, addressed the American Congress on Obstetrics and Gynecology, Cleveland, September 14, 1939, on "The Menopause

and Its Treatment." On September 15, 1939, Dr. Werner was the guest speaker of the Wisconsin State Medical Society at its annual meeting at Milwaukee. The title of his address was "The Sex Hormones." There was also a two-hour round table discussion on this subject.

The Fifth Annual Meeting of the Mississippi Valley Medical Society was held at Burlington, Iowa, September 27-29, 1939. Dr. Sinclair Luton, F.A.C.P., St. Louis, conducted a scientific exhibit on "Digitalis' Major Dosage Error (Difference between Drop and Minims)."

Dr. John W. Shuman, Sr., F.A.C.P., Los Angeles, received the degree of Doctor of Science as conferred by Geneva College last June.

Dr. Marcus W. Newcomb, F.A.C.P., Browns Mills, N. J., superintendent for twenty years of Fairview Sanatorium, Burlington county tuberculosis hospital, was recently honored for his activity in tubercular research by more than four hundred persons at a testimonial dinner.

Dr. Joseph C. Doane, F.A.C.P., Philadelphia, on September 20 delivered the introductory address to the student body of the Woman's Medical College of Philadelphia at the opening of the ninetieth college year of that institution.

Dr. J. Winthrop Peabody, F.A.C.P., Washington, D. C., resigned recently as superintendent and medical director of the Glenn Dale Sanatorium to devote his full time to medical practice. Dr. Peabody was succeeded by Dr. Daniel Leo Finucane, F.A.C.P., who had previously acted as assistant superintendent.

Among guest speakers at the annual meeting of the Indiana State Medical Association, at Fort Wayne, October 10-12, were the following:

- Dr. Byrl R. Kirklin, F.A.C.P., Rochester, Minn., "Some Contributions of the Roentgen-Ray to Advances in Diagnosis";
Dr. Emmet F. Horine, F.A.C.P., Louisville, Ky., "Psychologic Factors in Heart Disease";
Dr. Paul D. White, F.A.C.P., Boston, Mass., "Diagnosis and Treatment of Cardiovascular Emergencies";
Dr. Raphael Isaacs, F.A.C.P., Ann Arbor, Mich., "Diagnosis and Treatment of Pernicious Anemia."
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Dr. Nathan B. Van Etten, F.A.C.P., New York City, President-Elect of the American Medical Association, was a speaker at the annual banquet.

Dr. Wardner D. Ayer, F.A.C.P., Clinical Professor of Medicine at Syracuse University College of Medicine, gave a course on organic neurology for the Schoharie County and Montgomery County Medical Societies on six successive Tuesdays, from September 26 to October 31. The course was given under the auspices of the committee on public health and education of the Medical Society of the State of New York.

Dr. Robert Wilson, F.A.C.P., Dean and Professor of Medicine at the Medical College of the State of South Carolina, was the recipient of the 1939 plaque for distinguished service to South Carolina, conferred by the American Legion.

Under the Presidency of Dr. Alexander F. Robertson, Jr., F.A.C.P., Staunton, the Medical Society of Virginia held its seventieth annual session in Richmond, October 3-5. Among speakers on the general sessions program were:

- Dr. Franklin M. Hanger, Jr., F.A.C.P., New York City, "Differential Diagnosis of Jaundice";
Dr. Eugene M. Landis, F.A.C.P., Charlottesville;
Dr. Henry B. Mulholland, F.A.C.P., Charlottesville, "The Use of Protamine Insulin in Treatment of Diabetes Mellitus";
Dr. Louis Hamman, F.A.C.P., Baltimore, a clinicopathologic conference.

On October 4, during the state medical meeting, the Virginia Fellows and Associates of the American College of Physicians held their annual regional meeting, details of which will be reported later.

Dr. Wilmar M. Allen, F.A.C.P., superintendent of the Hartford Hospital, Hartford, Conn., has been appointed by the Governor of Connecticut as a member of a commission on the treatment and care of people of the state afflicted with physical or mental disabilities.

Dr. Soma Weiss, F.A.C.P., Hersey professor of the theory and practice of physic, Harvard Medical School, Boston, delivered an address on "Syncope, Collapse and Shock—Mechanism and Treatment" before a joint meeting of the Institute of Medicine of Chicago and the Chicago Society of Internal Medicine, October 27.

The University of Minnesota Medical School, Minneapolis, celebrated its fiftieth anniversary, October 12-14, with a program including clinics, round table discussions, and formal addresses. Dr. Anton J. Carlson, F.A.C.P., Chicago, delivered an address on "The Rôle of the Fundamental Sciences in Medical Progress" and Dr. Thomas Parran, F.A.C.P., Surgeon General of the U. S. Public Health Service, Washington, delivered an address on "Medical Education, Research and the Public Health."

Dr. Bryan M. Riley, F.A.C.P., Omaha, has retired as Dean of Creighton University School of Medicine, being succeeded by Dr. Charles M. Wilhelmj. Dr. Riley had served part time for the past six years as Dean. Dr. Wilhelmj will devote his full time to the work.

Dr. Joseph M. Hayman, Jr., F.A.C.P., has been promoted to Professor of Clinical Medicine and Therapeutics at Western Reserve University School of Medicine.

Under the Presidency of Dr. Charles S. Holbrook, F.A.C.P., New Orleans, the Southern Psychiatric Association held its annual meeting at Louisville, Ky., October 9-10. Among the speakers were:

- Dr. John W. Scott, F.A.C.P., Lexington, Ky., "An Internist's Reaction to the Psychoneuroses";
Dr. Oscar O. Miller, F.A.C.P., Louisville, Ky., "Psychiatric Medicine."

Dr. Oscar A. Sander (Associate), Milwaukee, and Dr. Albert E. Russell, F.A.C.P., U. S. Public Health Service, Chicago, delivered papers on "Metal Fume Poisoning" and "Syphilis Control and Its Relation to the Food Industry," respectively,

before the twenty-eighth annual session of the National Safety Congress at Atlantic City, October 16-20.

FELLOWSHIPS AVAILABLE IN PSYCHIATRY

The National Committee for Mental Hygiene (Dr. George S. Stevenson, 50 W. 50th St., New York City) has announced a limited number of fellowships, provided by the Commonwealth Fund and other sources, for training in extramural, especially child, psychiatry. Fellows will be assigned for one or two years to selected child guidance clinics, the term and plan for each to be determined by his needs. Candidates should have had at least two years of psychiatry in an approved mental hospital, in addition to qualities fitting them for extramural service.

Among the speakers on the program of postgraduate study, sponsored by the Arkansas State Medical Society, at the University of Arkansas School of Medicine, Little Rock, October 10-11, were:

- Dr. Edgar V. Allen, F.A.C.P., Rochester, Minn., "Occlusal Disease of the Peripheral Arteries";
Dr. Oliver C. Melson, F.A.C.P., Little Rock, Ark., "The Rôle of the Internist in the Care of Patients with Thyroid Disease";
Dr. Robert L. Schaefer, F.A.C.P., Detroit, Mich., "Clinical Indications of Anterior Pituitary-Like Sex Hormone";
Dr. Paul F. Stookey, F.A.C.P., Kansas City, Mo., "Diagnosis and Treatment of Meningitis."
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Dr. William Goldring, F.A.C.P., New York City, addressed the Academy of Medicine of Northern New Jersey at Newark, October 19, his subject being "Clinical Aspects of Hypertension and Arterial Heart Disease."

Dr. George W. Thorn, F.A.C.P., Baltimore, Md., addressed the naval medical and dental officers on duty in the vicinity of the District of Columbia, October 9, on "Supportive Treatment of Infections."

Dr. Walter L. Treadway, F.A.C.P., U. S. Public Health Service, San Francisco, on October 18, delivered a lecture on "The Poor, the Sick, the Bad" at the Mount Zion Auditorium, San Francisco, under the auspices of the Mental Hygiene Society of Northern California.

The Illinois State Medical Society has announced a new program of postgraduate education, to include several one-day conferences and to be held in various cities of the state. The first conference was scheduled for Jacksonville, Ill., November 9, and among the contributors appeared the names of Dr. Robert S. Berghoff, F.A.C.P., Chicago, Heart Disease; Dr. Julius H. Hess, F.A.C.P., Chicago, Pediatrics; Dr. James H. Hutton, F.A.C.P., Chicago, Endocrinology.

Dr. Frank H. Krusen, F.A.C.P., Rochester, Minn., was named Vice-President of the newly organized Society of Physical Therapy Physicians during its organization meeting in September. The membership in this new society is to be restricted wholly to physicians who devote their practice exclusively to physical therapy. Membership is to be limited to one hundred bona fide specialists who have devoted at least

five years to this specialty and have held or are holding teaching and directoral positions in physical therapy. The president and president-elect are, respectively, Dr. Frank H. Ewerhardt, St. Louis, and Dr. William Bierman, New York City.

Dr. Charles W. Dunn (Associate), Philadelphia, addressed the Medical Society of Delaware at Wilmington, October 9, on "Hormone Therapy: Uses and Abuses."

Dr. LaRue Carter, F.A.C.P., Indianapolis, Associate Professor of Neuropsychiatry at Indiana University School of Medicine, has been named chairman of the division of neurology at that institution.

Dr. Henry N. Tihen, F.A.C.P., Wichita, Kan., has been appointed to the medical advisory committee of the Norton Sanatorium for Tuberculosis.

Dr. Joseph O. Weilbaecher, Jr. (Associate), has been named an assistant director of the Charity Hospital, New Orleans.

Dr. Robert H. Riley, F.A.C.P., Baltimore, and Dr. Ridgely W. Baer, F.A.C.P., president of the Frederick County Medical Society, addressed the semi-annual meeting of the Medical and Chirurgical Faculty of the State of Maryland at Braddock Heights, September 28. Dr. Victor F. Cullen, F.A.C.P., superintendent and medical director of the Maryland Tuberculosis Sanatoria, was acting president of the faculty and delivered the address of welcome.

Dr. William D. Stroud, F.A.C.P., Philadelphia, delivered an address on "Coronary Disease Including Angina Pectoris and Its Differential Diagnosis from Gallbladder Disease; the Indications for Digitalis and Its Administration" before a graduate clinic, August 9, at the Robert Packer Hospital, Sayre, Pa.

Dr. Horace K. Richardson, F.A.C.P., of The Austen Riggs Associates, Stockbridge, Mass., delivered the annual address on "Mental Hygiene in the College Student" at Vassar College on October 2, 1939.

Dr. Harold G. F. Edwards, F.A.C.P., Shreveport, addressed the members of the Third International Cancer Congress at Atlantic City, Sept. 11 to 15, his subject being "Carcinoma of the Cervix; A Study of 656 Cases."

OBITUARIES

DR. EMIL GEORGE VRTIAK

Dr. Emil George Vrtiak (Associate), Chicago, Ill., died August 7, 1939, of coronary occlusion.

Dr. Vrtiak was born in Czechoslovakia, March 17, 1890. He received the bachelor degree from the University of Illinois in 1917, and the medical degree from Rush Medical College in 1920.

For many years Dr. Vrtiak had been interested in arthritis and in addition to studies made in the Clinic he returned for European study in 1924

and 1929. Dr. Vrtiak was an excellent teacher and at the time of his death was Associate Professor of Clinical Medicine at Rush Medical College.

He was a member of the staff of the Lutheran Deaconess Hospital and the Norwegian-American Hospital. He was a member of a number of medical societies including the American Medical Association, the American Association for the Study and Control of Rheumatism, the Bohemian Medical Society of Chicago, of which he was past president, and the Institute of Medicine of Chicago, and had been an Associate of the American College of Physicians since 1936.

Dr. Vrtiak was a hard worker, a thorough student, and an excellent doctor. In addition to care of patients, he did much for the welfare of the Czechs in Chicago. His patients recognized not only his medical interest in their difficulties but his extremely human attitude and his concern for their welfare.

ERNEST E. IRONS, M.D., F.A.C.P.

DR. JOHN A. MACGREGOR

The death of Dr. Macgregor occurred suddenly at his home in London, Ontario, on September 20, 1939, and with his passing the University of Western Ontario has suffered a serious loss, for Dr. Macgregor had been a strong stabilizing influence in the medical school and wielded a powerful influence over the student body.

Dr. Macgregor was born in Lanark County, Ontario, and graduated from University of Western Ontario Medical School in the Class of 1892 at the age of nineteen years.

Following his graduation he was a demonstrator at the medical school for one year, and then he established a general practise at Kent Bridge, near Chatham. He later practised for a time at Minden, Nebraska, and finally returned to London, Ontario, in 1905.

Following his return to London he became professor of pathology and bacteriology at the Medical School and in 1920 he was promoted to the post of Professor of Medicine. In 1925 he was made professor emeritus.

His contributions in the field of medicine were many and as a member of various medical associations he became well known in the profession.

Dr. Macgregor was a Fellow of the American College of Physicians, and a member of the American Medical Association and the Canadian Medical Association, and was a past president of the Ontario Medical Association. He was also a Fellow of the Royal College of Physicians (Canada).

In 1931 his valued contributions to the University of Western Ontario were formally recognized when he received the degree of LL.D.

Dr. Macgregor is survived by his wife, Mrs. Matilda (Langford) Macgregor, and one son, Dr. L. S. Macgregor of Kitchener, Ontario.

J. H. HOLBROOK, M.D., F.A.C.P.,
Governor for Ontario.

DR. HAROLD LEVI RYPINS

Dr. Harold Levi Rypins, F.A.C.P., of Albany, N. Y., died on August 25, 1939, at the age of forty-five years.

Dr. Rypins was born on December 21, 1891 at Evansville, Indiana. He received his A.B. degree from the University of Minnesota in 1914; attended Columbia University School of Journalism and then received his M.D. degree from Harvard University Medical School in 1919. He was Assistant Professor of Medicine at the Albany Medical College and was formerly an Associate and Instructor in Medicine there. He was Instructor in Medicine at the University of Minnesota Medical School in Minneapolis from 1920 to 1923; Secretary of the New York State Board of Medical Examiners; past President of the Federation of State Medical Boards of the United States; Member of the National Board of Medical Examiners; Member of the Executive Committee of the Advisory Council on Medical Education; Executive Secretary of the Medical Grievance Committee of the State Education Department; Fellow of the American Medical Association and Fellow of the American College of Physicians since 1934.

Dr. Rypins is survived by his widow, three children and a host of friends throughout the country.

CHARLES F. TENNEY, M.D., F.A.C.P.,
Governor for Eastern New York.

DR. GEORGE HOLT BARKSDALE

Dr. George Holt Barksdale, F.A.C.P., Charleston, W. Va., was born in Alderson, Monroe County, West Virginia, August 15, 1882; died October 8, 1939, of a heart attack at his home in Charleston.

Dr. Barksdale received his M.D. degree from Northwestern University Medical School in 1908. He served his internship in St. Luke's Hospital, Chicago, and received postgraduate training at St. Luke's Hospital, Chicago, Massachusetts General Hospital, Walter Reed Hospital, Washington, D. C., New York Neurological Institute, and in Vienna. He was formerly Assistant to Owner, Fabiola Hospital, Eveleth, Minn., and Director, Hill Crest Sanitarium, Charleston. He was a member of the Staff of St. Francis and Charleston General Hospitals; author of several publications; and during the World War served as Chief of Medical Service and Chief of the Tuberculosis Board at U. S. Army General Hospital 42, Spartanburg, S. C., with grade of Major, Medical Corps.

Dr. Barksdale was a member of the Kanawha County Medical Society, West Virginia State Medical Association and the American Medical Association. He was ex-President and ex-Vice President of the West Virginia Heart Association; ex-President of the Charleston Journal Club; ex-President and Member of the West Virginia Tuberculosis and Health Associa-

tion; and had been a Fellow of the American College of Physicians since 1936.

Dr. Barksdale is survived by his wife, two sons and one daughter.

ALBERT H. HOGE, M.D., F.A.C.P.,
Governor for West Virginia.

DR. THADDEUS WALKER

Dr. Thaddeus Walker, of Detroit, Michigan, an Associate of the American College of Physicians since 1926, died June 13, 1939. He was born in Walkerville, Ontario, in 1869. Following graduation from the Detroit College of Medicine in 1893, he spent three years in graduate work in Berlin, Vienna, and Edinburgh. On his return, he started practice in Detroit, and as his interest lay largely in pathology and clinical laboratory procedures, he founded the Detroit Clinical Laboratory, the first of its kind in the city.

Dr. Walker served during the Spanish American War as a Contract Surgeon. He retired from active practice in 1912. He was an Honor Member of the Wayne County Medical Society, which he had ably served in its earlier days of growth and expansion. He also held membership in the Detroit Academy of Medicine.

Dr. Walker's passing will be mourned by a host of friends, as well as by his professional colleagues of the city.

HENRY R. CARSTENS, M.D., F.A.C.P.,
Governor for Michigan.

DR. BAYARD G. KEENEY

Dr. Bayard G. Keeney, F.A.C.P., Shelbyville, Ind., died suddenly on October 11 while attending the annual convention of the Indiana State Medical Association in Fort Wayne, aged 63 years.

Dr. Keeney was to have served as Chairman of the Section on Medicine of the State Association at the Wednesday afternoon Session, and his son, Dr. Edmund L. Keeney, of Baltimore, was to have been one of the guest speakers on the Thursday morning program.

He received his M.D. degree from the University of Cincinnati College of Medicine in 1902, and then did postgraduate work in Europe.

Dr. Keeney was Shelby County Health Commissioner for six years, and always was active in civic and medical society work. He was a member of the Shelby County Medical Society, Indiana State Medical Association and the American Medical Association, and had been a Fellow of the American College of Physicians since 1930.

ROBERT M. MOORE, M.D., F.A.C.P.,
Governor for Indiana.

ANNALS OF INTERNAL MEDICINE

VOLUME 13

DECEMBER, 1939

NUMBER 6

EPIDEMIC INFLUENZA: STUDIES IN CLINICAL EPIDEMIOLOGY *

By THOMAS FRANCIS, JR., M.D., *New York, N. Y.*

ALTHOUGH based on well recognized modes of action, clinical epidemiology as a scientific concept has but recently evolved.^{1, 2} It has its origins, on the one hand, in the type of epidemiology which interests itself not only in the manner in which an epidemic arises but also in the varying characteristics of the epidemic disease in the affected individuals. On the other hand, its roots extend, as Paul² has pointed out, into the heart of family practice where the physician dealing primarily with the sick individual attempts to study the patient in relation to his familial or communal setting.

The trend has been for epidemiology to become increasingly statistical, minimizing the clinical method. Data are obtained by sheer power of quantitation whereas the more specific and delicate qualitative procedures are neglected. The conclusions become less authentic unless the disease presents some gross pathognomonic sign which, as the rash in scarlet fever, serves to identify it. Here, too, individuals undergoing the same bacterial infection without exhibiting the characteristic exanthem may not be included in the data, and an entirely false concept of the incidence of the specific infection is obtained.

Epidemiology has grown to consider the herd as its unit for study; clinical investigation, the individual. Since the behavior of the herd must comprise an integration of the influences affecting its individual members, clinical epidemiology would represent something of a compromise between these two points of view. It would consider the individual case within the epidemic and, by the application of the methods of clinical investigation to the study of disease in its natural habitat, would build on a surer ground, while dealing in smaller numbers, information which could subsequently serve as the basis for accurate epidemiological conclusions. This method has established our present day knowledge of diphtheria on a plane scarcely approached in any other type of infectious disease.

* Read at the New Orleans meeting of the American College of Physicians March 28, 1939.

The use of the same concept as an approach to the study of epidemic influenza is especially pertinent for two reasons: (1) because of the great confusion in the diagnosis of respiratory infection on etiological, clinical or epidemiological grounds; (2) because of the epidemiological assumption that all these outbreaks are the same disease. To study epidemic influenza on any basis other than that of investigating it in detail would only result in emphasizing again unjustified assumptions, the truth concerning which constitutes one of our major problems.

The studies I should like to discuss will serve to illustrate the mode of introduction of clinical epidemiology to the particular problems at hand. They have been directed toward isolation of the causative agent; toward the establishment of a critique for diagnosis of epidemic influenza and establishing it as a disease entity; toward attempts to determine whether all outbreaks of clinical similarity are the same disease; toward determining whether all illness of similar clinical characteristics occurring in the course of an epidemic is the same, and whether all infections caused by the same agent present the same clinical picture. I shall summarize briefly the evidence obtained in recent years which relates to these questions.

THE IDENTIFICATION AND DIAGNOSIS OF EPIDEMIC INFLUENZA

The causative agent of epidemic influenza has been clearly established as a specific filterable virus.³ In sharp contrast to the observations of Shope regarding swine influenza, there has been no evidence accumulated in the course of these investigations to indicate that a bacterium of the *H. influenzae* type has played any rôle whatever in the observed epidemics of human influenza. The virus was first isolated in 1933 by Smith, Andrewes, and Laidlaw in ferrets inoculated intranasally with the nasal washings of patients suffering from epidemic influenza. In the ferret the disease produced was essentially a febrile reaction associated with injury to the nasal turbinate tissues. The following year I succeeded in isolating the virus from human throat washings obtained during an epidemic in Puerto Rico and later in the United States. It was found possible, in transferring the disease from ferret to ferret by means of suspensions of lung tissue, to induce a more severe disease with an extensive and sometimes fatal pneumonia. In both laboratories at this time the virus was successfully transferred to mice by the intranasal inoculation of virus-containing material from an experimentally infected ferret. The mice developed a highly fatal pneumonia, involving the entire lung, caused by virus alone without bacterial assistance. When given by routes other than the intranasal, the virus does not cause infection.

Smith, Andrewes and Laidlaw had already reported that the serum of recovered animals and of human individuals, when mixed with the virus before injection, was capable of protecting normal ferrets from virus infection. The demonstration of the susceptibility of mice provided an animal which could be used in relatively large numbers for experimental studies.

The pulmonary lesions produced by the virus were utilized in devising a test for the antibody content of a serum. Mixtures of dilutions of serum and constant amounts of virus were instilled into the nostrils of anesthetized mice. It was noted that the serum of a ferret recovered from infection would, under these conditions, protect the mice from pneumonic invasion whereas mice receiving mixtures of normal serum and virus would die uniformly. We then demonstrated with this technic that human individuals recovering from the disease developed a marked increase in the antibody titer of the blood in convalescence as compared with the titer of the serum of the same individual taken during the acute stage of illness. But it was also found that the sera of a large proportion of the population possessed a significant amount of antibody to the virus. In contrast to the frequent difficulty encountered in demonstrating antibodies to viruses, we had an overabundance.

Subsequently, it was found that antibodies could be detected by the complement fixation reaction as well. Extracts of infected mouse lungs or tissue culture fluid served as antigen which reacted with immune serum. These procedures, namely, isolation of virus and serological tests, were then available for the detailed study of epidemics. The significance of the virus had already been established by its isolation throughout the world in the years 1934 and 1935. In addition to New York and London, virus was recovered from epidemic outbreaks in Philadelphia, New Haven, Alaska, Australia and Moscow. Moreover, in Australia and Moscow confirmatory evidence was obtained to substantiate the probable significance of the rise in antibodies in the serum of selected patients. But the reliability of these technics in the diagnosis of individual cases within an epidemic was not known; hence, the building up of a composite picture of an epidemic on authentic data had not been accomplished. This we attempted in the winter of 1936-1937 when an epidemic of moderate severity swept throughout the northern hemisphere and when virus was isolated in many laboratories throughout the world. During the epidemic period from December 1936 to March 1937 we had the opportunity to study material, consisting of specimens of throat washings, blood, or both, from 120 patients suffering from respiratory infection. A diagnosis of epidemic influenza was made in 100 of these cases. From 64 of the latter, throat washings were obtained and virus was recovered from 52 or 81 per cent of them by ferret inoculation, by direct transfer to mice, by direct inoculation of the throat washings into tissue culture or onto the chorio-allantoic membrane of the developing chick. When parallel neutralization and complement fixation tests were carried out with the acute and convalescent sera of the patients from whom virus was recovered, it was found that a uniform 10 to 20-fold rise in antibodies to the virus occurred during recovery. The uniformity of the serological results in cases of disease proved by the recovery of virus was sufficient to warrant the utilization of the reactions as diagnostic procedures in those cases in which virus was either absent or in which attempts to isolate it were unsuccessful. Thus, in 48

patients the results of serological studies enabled one to make the diagnosis of epidemic influenza. Otherwise the diagnosis would have been based on clinical observations alone or, because of the failure to recover virus, the patient would have been dismissed from the group of authentic cases.

Since the symptom complex which characterizes influenza in the individual is common to the early stages of numerous infections, the clinical criteria have not been sufficiently accurate to permit confident diagnosis. Furthermore, the mere presence of an epidemic colors the physician's diagnostic vision. The development of laboratory aids to diagnosis was, therefore, an imperative need to be fulfilled before further advance could be made. The studies described above have revealed the manner in which the validity of procedures devised for this purpose was established. The use of these methods in conjunction with clinical and epidemiological observations has succeeded in delineating a specific disease of virus etiology from the limbo of upper respiratory infections.

DIFFERENTIAL DIAGNOSIS

I should like now to demonstrate the manner in which these same criteria can serve the problem of differential diagnosis of cases of respiratory infection occurring in the course of a single epidemic and aid in distinguishing between the epidemics of respiratory disease which prevail in different years.

During the epidemic of 1936-1937 patients were observed whose symptoms were in many respects similar to those noted in the proved cases of influenza. Nevertheless, there were certain clinical differences: some of them had hemolytic streptococcal tonsillitis; some of them had atypical pneumonias in which bacterial pathogens were involved, but which nevertheless were considered representative of the so-called influenzal relapses; others had low grade febrile infections with bronchitic signs, whereas still others had afebrile common colds. Our problem was to determine whether these were also instances of infection due to the virus of epidemic influenza as was suggested by their occurrence in the midst of the epidemic. The same methods were, therefore, utilized in the analysis of these illnesses.

We were entirely unsuccessful in isolating virus from them and failed, except in one case which was called Type III pneumococcus bronchitis, to demonstrate the rise in antibodies against standard virus which characterized the cases of influenza. On the other hand, in five cases of atypical pneumonia or relapses the evidence obtained indicated that the so-called relapses were not relapses of influenza virus infection but represented superimposed bacterial infections developing in the period of convalescence from the virus infection. In each there had been a period of moderate illness, with a sudden recrudescence, 7 to 12 days after the onset. The antibody titers to influenza virus had at the time of the relapse already reached their maximum and were at levels which had been shown to typify the influenzal convalescent. Thus, the pneumonias observed were clearly not attributable to the virus

except as it produced the primary tissue damage. The remaining cases represented illnesses entirely unrelated to epidemic influenza. The experimental data furnished authoritative answers to what otherwise would have been sources of sharp disagreement in clinical interpretation.

The accuracy of the diagnostic methods in differentiating instances of influenza virus infection from other types of respiratory disease occurring at the same time is quite striking. Let us see how these procedures can be used to further advantage in discriminating between epidemics of respiratory infection occurring in different years but possessing highly comparable clinical and epidemiological characteristics. Stuart-Harris, Andrewes and Smith (monograph) have reported details of three small localized outbreaks of influenza-like disease which they have termed "febrile catarrh" and in which no evidence could be gathered to relate the disease, etiologically, to the virus of epidemic influenza. These infections were, in the majority of instances, associated with acute tonsillitis and pharyngitis with the presence of either follicular or slimy purulent exudate. Hemolytic streptococci were implicated, but not uniformly recovered. In no case was the virus of epidemic influenza demonstrable.

In the early months of 1936 we encountered and studied, especially in California, an extensive outbreak of a disease which to the best of my clinical judgment was indistinguishable from the epidemics which have yielded the characteristic virus results. Approximately 30-40 per cent of the population was affected, and 50-60 per cent of the cases occurred in the age group of the population under 20 years of age. The epidemic was abrupt in its appearance in a community, reached its peak in one to two weeks and subsided rapidly. There was no leukocytosis. From a large number of throat washings intensively studied, we were unable to isolate the virus of epidemic influenza. Bacteriological studies yielded no noteworthy information. When the capacity of the serum of these patients to neutralize influenza virus was tested, in sharp contrast to the chain of events observed in influenza, there was no detectable difference between the titers of the sera taken in the acute phase of illness and those taken from the same patients in convalescence. We have here a striking example of a widespread epidemic of influenza-like disease which was shown—by negative results, it is true—to be entirely different etiologically. During the period of study a new virus was recovered from animals inoculated with the throat washings of the patients.⁴ This virus differs sharply in its pathological and immunological characteristics from that of influenza. In addition to producing pneumonia after intranasal infection, inoculation of mice by other routes causes a mononuclear meningitis. We have not as yet, however, conclusively established whether the meningo-pneumonitis virus was derived from the human population or from the ferrets. We have not encountered it since the early 1936 epidemic.

Last year we again failed to isolate influenza virus during the respiratory disease season. This winter, although there has been no real epidemic in

our district, there have been numerous cases of relatively mild febrile disease; in some areas the incidence has reached high proportions. We have not succeeded in recovering typical influenza virus. Nor, on the basis of conversations with other workers, has this been successfully accomplished elsewhere to any significant degree. Most of the cases we have seen have corresponded more closely to the Woolwich type of epidemic reported by the English investigators. Laryngitis, tonsillitis and pharyngitis with exudate have been common—not always associated with hemolytic streptococcus infection.

This is all very well, you may say, but what assistance does it afford to the clinician who must see his patients, attempt to make a diagnosis, and treat them at the time they take sick rather than waiting for recovery to occur so that the serum may be tested for antibodies? The first laboratory confirmatory evidence, a febrile reaction in the ferret inoculated with the patient's throat washings, would not occur for 48 hours, and antibodies in the serum do not show significant changes in amount until after the patient's fever has subsided. The first requisite in attempting to furnish clinical aids is an accurate record of the patient's state to be used in conjunction with the laboratory studies. In the progress of the experimental studies of influenza considerable effort has been directed toward attempts to discern clinical features sufficiently striking to approach a pathognomonic level. By comparing the nature of cases proved by experimental laboratory procedures to be epidemic influenza with those similarly shown not to be, certain conclusions have been reached.

There is no reason to believe that epidemic influenza is etiologically related to the common cold, either in its acute afebrile stage with characteristic running nose or in its later stages when febrile bacterial complications ensue. In fact we have frequently found that a common cold has occurred in the patient two to three weeks before the onset of influenza and is readily differentiated by the patient himself. Influenza is sharply different from acute pharyngitis and tonsillitis of bacterial origin in which purulent exudate is present in the throat and in which leukocytosis commonly occurs.

Stuart-Harris has tabulated the essential clinical characteristics which typify epidemic influenza and tend to differentiate it from the diseases termed febrile catarrhs. With one or two modifications I should like to reproduce the table here. One of the first factors in identifying epidemic influenza apart from its distribution is the character of the onset. The onset is sudden with chills or chilliness, prominent headache and constitutional symptoms. The fever rises rapidly. Respiratory symptoms are not striking at first, being limited to a feeling of burning or rawness in the nasopharynx. Cough may be slight but usually increases. The white blood count is normal or reduced, rarely increased. The course of the disease is also characteristic in usually presenting a three day fever followed by a prolonged convalescence. Vague pulmonary suppressions may be noted and roentgen-ray may reveal a moderate bronchiolitis in many instances. These criteria may seem

vague but in fact if the clinician will make the effort to utilize them rather than to group all the diseases in a hodge-podge, a working classification can be had. The studies are still young and it is not unlikely that further laboratory methods applicable to early diagnosis will be devised.

DIFFERENTIAL DIAGNOSIS OF EPIDEMIC INFLUENZA AND FEBRILE CATARRHS

	Epidemic Influenza	Febrile Catarrhs
Onset.....	Sudden with chills	Insidious
Symptoms.....	Constitutional symptoms preponderate	Respiratory symptoms preponderate
Headache and myalgias....	Prominent	Vague
Cough.....	Short and dry	Paroxysmal, irritating, painful, often productive
Nose.....	Nasopharyngeal irritation	Stuffiness
Voice.....	Husky	Hoarse
Throat.....	Posterior pharyngitis; no exudate	Tonsillitis as well as pharyngitis; exudate common
Fever.....	Sometimes diphasic	Rarely diphasic
Complications.....	Bronchiolitis and pneumonia	Bronchitis or bronchopneumonia
Epidemic.....	Short with rapid "peaking"	Prolonged and "grumbling"
Contacts.....	Clinical picture uniform although graded in severity	Clinical picture variable with frank tonsillitis in contacts
Leukocyte count.....	Leukopenia common	Not diagnostic
Virus.....	Influenza virus recoverable from pharynx	Influenza virus not concerned
Course.....	Short	Apt to be prolonged

(Modified after Stuart-Harris.)

I have mentioned briefly the common clinical features of epidemic influenza, but does it necessarily follow that infection with epidemic influenza virus always elicits a similar type of clinical disease? On the basis of studies in experimental animals a negative reply may be given. The severity of the infection may be modified either by the strength of the infecting agent or by the degree of immunity of the animal. Moreover, in an institution where an epidemic was in progress, a study of human individuals, who were intimately exposed to infection but who showed no clinical evidence of infection, was made. It was found by repeated examination of the influenzal antibody content of the serum of each of these contacts during the epidemic period that approximately 10 out of 48 underwent influenza virus infections of subclinical intensity. Furthermore, from a few cases virus was recovered, although the signs and symptoms of disease were so mild that they actually represented examples of inapparent infection or of subclinical carriers of infection. Nevertheless, in these patients the diagnostic increase in antibody titer occurred.

Up to the present there is no evidence that the differences observed in different patients or in different years are related simply to differences in virulence of the prevalent strains of virus, or that differences in the antigenic make-up of the virus strains are responsible. We *can* say that not all people who, on the basis of serological evidence would be considered sus-

ceptible, come down when exposed, and that not all who might be thought to be resistant, escape. The duration of immunity is not known, but I am convinced that it is much longer than is generally thought to be the case, and that stories of attacks of influenza two or three times each winter, or even every winter, are rarely, if ever, true.

Many factors remain to be studied; many obstacles must be overcome before the entire field of acute virus diseases of the respiratory tract will be charted. The application of clinical epidemiological methods must be the manner in which it is done. By comparing the clinical differences in patients and epidemics with specific laboratory data, the various entities will fall into their proper places in the puzzle of epidemic respiratory disease.

We have already succeeded in this manner in bringing from the field of common cold, grippe, tonsillitis, and "febrile catarrhs" a disease entity, clinically and epidemiologically epidemic influenza. This disease has been shown to have a specific etiological agent, a filterable virus, which has a striking affinity for the respiratory tract. It has been shown to reflect its visitation in definite antibody responses which can be readily measured and can serve as diagnostic aids just as accurately as those employed in the diagnosis of bacterial diseases. Utilization of the laboratory aids has made it possible to show that all illnesses of similar clinical aspects occurring in the course of an epidemic do not represent the same disease—and that all the waves of respiratory infection which occur from year to year are not epidemic influenza but may be entirely different diseases etiologically. They bear no more relation to one another than typhoid fever and typhus fever. The studies which have served to bring the disease, epidemic influenza, into sharp focus can also serve as a reference point in establishing the nature of the unidentified mimics. Statistics have failed; clinical observations have not sufficed; but clinical epidemiology, properly applied offers great promise of things to come.

BIBLIOGRAPHY

1. FRANCIS, T., JR.: Immunology of epidemic influenza (De Lamar lecture), *Am. Jr. Hyg.*, 1938, xxviii, 63.
2. PAUL, J. R.: President's address; clinical epidemiology, *Jr. Clin. Invest.*, 1938, xvii, 539.
3. For detailed reports and bibliography see:
 - (a) FRANCIS, T., JR.: Epidemiological studies in influenza, *Am. Jr. Pub. Health*, 1937, xxvii, 211.
 - (b) FRANCIS, T., JR., MAGILL, T. P., RICKARD, E. R., and BECK, M. D.: Etiological and serological studies in epidemic influenza, *Am. Jr. Pub. Health*, 1937, xxvii, 1141.
 - (c) STUART-HARRIS, C. H., ANDREWES, C. H., and SMITH, W. S., with D. K. M. CHALMERS, E. G. H. COWEN, and D. L. HUGHES: A study of epidemic influenza: with special reference to the 1936-7 epidemic, *Med. Res. Council, Spec. Rep. Series*, No. 228, 1938, H. M. Stationery Off., London.
4. FRANCIS, T., JR., and MAGILL, T. P.: Unidentified virus producing acute meningitis and pneumonitis in experimental animals, *Jr. Exper. Med.*, 1938, lxxviii, 147.

A NOTE ON THE MECHANISM OF SPONTANEOUS PNEUMOTHORAX *

By LOUIS HAMMAN, M.D., F.A.C.P., *Baltimore, Maryland*

SPONTANEOUS pneumothorax has become a well established clinical condition. The characteristic features are the sudden occurrence of pneumothorax in apparently healthy persons, which clears up uneventfully, and is not accompanied by pleural exudate, by fever, or by other constitutional symptoms. It occurs chiefly in early adult life, more often in men than in women.

Thirty years ago when spontaneous pneumothorax first began generally to be recognized, it was thought to be a symptom of pulmonary tuberculosis. Even though the presence of tuberculosis could not be demonstrated still the pneumothorax was looked upon as a precursor of manifest tuberculosis, just as we regard pleurisy with effusion as evidence of tuberculous disease. The mechanism responsible for the occurrence of pneumothorax was seldom precisely stated but by inference we were led to conclude that it was due to the rupture of a small subpleural focus of tuberculosis. These views are no longer tenable. In the first place when a tuberculous focus ruptures into the pleural cavity an entirely different group of symptoms appears; there is violent reaction of the pleura accompanied by pronounced constitutional symptoms. Again, prolonged observation has demonstrated that patients who have had spontaneous pneumothorax do not later in life become tuberculous, at least only an occasional one does, a proportion not in excess of the incidence of tuberculosis in the general population. Yet again, the presence of pulmonary tuberculosis has not been demonstrated in any of the cases which have been examined post mortem. It is true that spontaneous pneumothorax may occur in the tuberculous and run the benign course that it does in those without the slightest evidence of disease of the lungs. When this happens we are forced to conclude that the pneumothorax is due not to the rupture of a focus of tuberculosis but to the same mechanism which causes pneumothorax in healthy persons.

Since nearly all patients with spontaneous pneumothorax promptly recover we seldom have the opportunity to investigate the cause of the pneumothorax. Kjaergaard, in 1932, after a laborious search of the literature discovered reports of nine autopsies upon patients with spontaneous pneumothorax. In six of these, emphysematous blebs, or, as he calls them, valve vesicles, were found protruding from the pleural surface, usually in the region of the apex, and in five a rupture of one of the vesicles was demonstrated. In the three remaining cases no cause for the pneumothorax was discovered, the lungs having been described as normal.

* Read at the New Orleans meeting of the American College of Physicians, March 30, 1939.

Kjaergaard was not fortunate enough to obtain a postmortem examination upon any of his 51 cases at a time when the pneumothorax was present and its cause could be explored, but stimulated by the published observations he began routinely to search at autopsy for the presence of pleural air vesicles and found two instances which he examined minutely. Both were very thin walled vesicles and in both he discovered a communication with a bronchiole, the communication being obstructed by a valve-like structure which allowed air to enter and inflate the vesicle but prevented it from escaping during expiration. In one case the valve was formed by a lapet of emphysematous lung tissue, in the other by a band of scar tissue, arrangements which he speaks of respectively as emphysematous valve vesicle and cicatricial valve vesicle. In one patient who had three attacks of spontaneous pneumothorax a large subpleural vesicle was plainly visible in the roentgenograms, a fact which Kjaergaard looks upon as presumptive evidence that the attacks of pneumothorax were due to rupture of the vesicle. Wilcox and Foster-Carter, in 1937, report the case of an air pilot who died in the third attack of pneumothorax. During life the roentgenograms indicated the presence of a large subpleural bulla at the base of the left lung. At the postmortem examination a large bulla measuring two inches in diameter was found but it was impossible to demonstrate any communication between the vesicle and a bronchus or between the vesicle and the pleural cavity.

A year after his first communication Kjaergaard published the report of two cases of pneumothorax found unexpectedly at autopsy in patients dying of other cause. In both instances many congenital cysts were present in the lungs, and in one instance the cyst that had ruptured was discovered. Therefore, Kjaergaard concludes that the probable cause of all instances of spontaneous pneumothorax is the rupture of subpleural valve vesicles which in origin are the result of: 1, localized emphysematous changes in the lung; 2, scar tissue in the lungs, or pleural adhesions; 3, congenital cystic disease of the lungs.

Since the publication of Kjaergaard's studies a number of postmortem examinations of spontaneous pneumothorax have been reported. In the case of Wilcox and Foster-Carter a large subpleural bulla was present but no evidence of rupture into the pleural cavity could be demonstrated. Priest records the sudden death of a healthy young sergeant from bilateral pneumothorax. At autopsy the lungs showed no evidence of disease; the pleural surfaces were normal in every respect. No pleural leak was found when water was forced through the main bronchi. In another instance of bilateral pneumothorax Hasney and Baum could find no site of rupture of the pleura on the left; on the right they discovered a ruptured emphysematous subpleural bleb. Schmincke found at autopsy, in still another case, a number of subpleural cysts but could not demonstrate that any of these had ruptured. Neffson and Bullowa report an instance of bilateral pneumothorax with subcutaneous emphysema in a child two years of age. The

pneumothorax and subcutaneous emphysema disappeared but a week later the patient died of pneumonia. At autopsy the lungs showed alternating areas of consolidation and atelectasis and the characteristic changes of interstitial pneumonia. The precise cause of the pneumothorax could not be demonstrated. In a number of cases of spontaneous pneumothorax coming on during pneumothorax treatment Cutler was able to demonstrate adhesions preventing the collapse of the lung. When these adhesions were cut, through the thoracoscope, the condition was promptly relieved. Cutler concludes that the pneumothorax was due to a small pleural tear produced by the pull of adhesions as the lung was collapsing.

During the past six years I have been interested in the spontaneous occurrence of interstitial emphysema of the lungs and mediastinal emphysema. The characteristic features of this condition may be summarized as follows:

Interstitial emphysema of the lung may occur without the least effort, when the patient is quietly standing, sitting or lying down.

When the air reaches the mediastinum, distending the mediastinal tissues, the patient complains of pain which is often very severe. Usually the pain is located beneath the sternum; sometimes it radiates to the back; at other times to the neck and shoulders, rarely to the arms. Accompanying the pain there is often a sensation of pressure or of expansion beneath the sternum.

There are no constitutional symptoms, no evidence of shock. The temperature, the pulse and respiratory rates, the blood pressure, the leukocyte count are very little if any altered.

In many instances a peculiar and distinctive sound is heard over the heart synchronous with the contractions. Usually the sound is heard only during systole but at times it may be heard also during diastole.

The area of cardiac dullness is diminished or completely obliterated, the dullness being replaced by a hyperresonant percussion note.

The roentgenogram is a valuable aid in establishing the diagnosis. In instances in which the characteristic sound over the heart is absent the roentgenographic evidence of air in the mediastinum may be decisive.

When air appears in the subcutaneous tissues of the neck the diagnosis is at once assured.

The matter of interest in the present connection is that pneumothorax occurred in two of the seven cases of spontaneous mediastinal emphysema which I have observed. That this is not an accidental association is attested by the fact that a number of other physicians have also noted their simultaneous appearance. There are only two possible ways in which the pneumothorax could occur, namely; the air might travel along the interstitial bands of connective tissue to the pleural surface and there produce a pleural vesicle which would later rupture; or, the air having reached the mediastinum might rupture through the thin mediastinal wall into the pleural cavity. There is direct experimental evidence and much circumstantial clinical evidence to support the contention that the second route is the one usually taken.

In animals it is a very simple matter to produce interstitial emphysema by inflating the lungs. If the inflation is continued pneumothorax occurs. Macklin's experiments on cats are reported in detail. At autopsy the lungs were carefully removed and he searched thoroughly for evidence of pleural rupture by reinflating the lungs and squeezing them under water. In not a single instance was he able to demonstrate the escape of air through a rent in the pleura. On the other hand in a number of cases he discovered the point of rupture in the delicate mediastinal wall.

The clinical evidence which supports the view that pneumothorax sometimes occurs by rupture of the mediastinal pleura consists of numerous observations upon the concomitant occurrence of pneumothorax and mediastinal emphysema. Kjaergaard admits the difficulty under these circumstances of explaining the pneumothorax as being caused by the rupture of a subpleural valve vesicle but does not suggest the possibility of rupture of the mediastinal pleura. A brief summary of these observations is as follows:

1. In trauma to one side of the chest, pneumothorax may occur on the opposite side. It is possible under these circumstances that the contralateral pneumothorax may be due to the rupture of a subpleural vesicle but it is more likely that interstitial emphysema is produced in the injured lung by rupture of alveoli and that the air having reached the mediastinum escapes into the pleural sac through a small rent in the delicate mediastinal membrane. The fact that in some of these cases there is also subcutaneous emphysema in the neck makes the second chain of events seem probable.

2. In children with pneumonia, and less commonly in adults, mediastinal emphysema often occurs, sometimes accompanied by subcutaneous emphysema in the neck, less often by pneumothorax. This association of clinical manifestations strongly suggests that the pneumothorax is caused by the escape of air from the mediastinum.

3. Subcutaneous emphysema and pneumothorax may occur simultaneously in attacks of asthma. Again under these circumstances one is justified in assuming that the pneumothorax may be secondary to the mediastinal emphysema.

4. Mediastinal emphysema sometimes occurs during treatment with artificial pneumothorax. It seems reasonable to suggest that spontaneous pneumothorax coming on during pneumothorax treatment especially when it occurs upon the opposite side, may in some cases be due to a tear in the mediastinum even though autopsy and thoracoscopic examination have demonstrated that in certain instances it has been due to the rupture of subpleural vesicles or a tear in the pleura produced by the pull of adhesions.

5. Lundie and Ljungdahl have each reported cases of pneumothorax alternating with pneumopericardium. In view of the observations on spontaneous mediastinal emphysema, previously referred to, one is justified in questioning the diagnosis of pneumopericardium. The clinical history and the sounds heard over the heart are altogether characteristic of mediastinal

emphysema. The pericardium is a tough membrane and it is a little difficult to believe that a subpleural air vesicle can rupture through it. Were the membrane thinned by inflammatory disease in the lung which would finally rupture through, then an entirely different train of symptoms would follow.

SUMMARY

Careful observation has demonstrated that spontaneous pneumothorax may be caused by: (1) the rupture of subpleural valve vesicles; (2) a rent in the pleura due to the pull of adhesions; (3) the rupture into the pleura of congenital pulmonary cysts. I wish to suggest a fourth cause, namely, rupture of the mediastinal pleura when there is mediastinal emphysema. This mechanism may prove to be a not uncommon one and I suggest that all patients developing spontaneous pneumothorax be carefully examined for evidence of the presence of mediastinal emphysema.

REFERENCES

- BERKLEY, H. K., and COFFIN, T. H.: Generalized interstitial emphysema and spontaneous pneumothorax as complications of bronchopneumonia, *Jr. Am. Med. Assoc.*, 1919, lxxii, 535.
- CUTLER, J. W.: Spontaneous pneumothorax complicating pneumothorax therapy, *Jr. Am. Med. Assoc.*, 1938, cxi, 408.
- ELLIOTT, R. W.: Subcutaneous emphysema and pneumothorax in bronchial asthma, *Lancet*, 1938, i, 1104.
- FAULKNER, W. B., and WAGNER, R. J.: Fatal spontaneous pneumothorax and subcutaneous emphysema in an asthmatic, *Jr. Allergy*, 1936, viii, 267.
- HAMMAN, L.: Spontaneous mediastinal emphysema, *Bull. Johns Hopkins Hosp.*, 1939, lxiv, 1.
- HASNEY, F. A., and BAUM, F.: Bilateral spontaneous idiopathic pneumothorax in apparently healthy individuals, *Radiology*, 1937, xxviii, 47.
- JOANNIDES, M., and TSOULOS, G. D.: The etiology of interstitial and mediastinal emphysema, *Arch. Surg.*, 1930, xxi, 333.
- KJAERGAARD, H.: Spontaneous pneumothorax in the apparently healthy, *Acta. Med. Scand.*, 1932, xliii, 1.
- KJAERGAARD, H.: Pneumothorax simplex, *Acta. Med. Scand.*, 1933, lxxx, 93.
- LJUNGDAHL, M.: Cited by Kjaergaard, H.
- LUNDIE, R. A.: Cited by Kjaergaard, H.
- MACKLIN, C. C.: Pneumothorax with massive collapse from experimental local over-inflation of the lung substance, *Canad. Med. Assoc. Jr.*, 1937, xxxvi, 414.
- MACKLIN, C. C.: The site of air leakage from the lung alveoli into the interstitial tissue during local over-inflation in the cat, *Verhandl. d. Anat. Gesellsch. Ergänzungsh. Anatomischer Anzeiger*, 1938, lxxxv, 78.
- NEFFSON, A. H., and BULLOWA, J. G. M.: Influenza with simultaneous bilateral spontaneous pneumothorax and subcutaneous emphysema, *Arch. Otolaryng.*, 1938, xxviii, 388.
- PRIEST, R.: Bilateral spontaneous pneumothorax, *Brit. Med. Jr.*, 1937, ii, 321.
- SCHMINCKE: Cited by Hasney, F. A. and Baum, F.
- WILCOX, A., and FOSTER-CARTER, A. F.: Spontaneous pneumothorax with bullous emphysema, *Lancet*, 1937, ii, 315.

CHANCRES STUDIED FROM THE PUBLIC HEALTH POINT OF VIEW *

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OUT of the large collection of case records in the syphilis clinics of the New York City Department of Health a sample of 15,090 records was taken at random from the active files, and studied to ascertain certain facts regarding the primary or chancre stage of syphilis in our clinic case load. Among the 15,090 case records were 971, or 6.43 per cent, indicating a definite diagnosis of chancre by the darkfield method at the time of admission to the clinic service. There were in addition, 7,386 records giving a definite history of chancres, 48.95 per cent of the total. Together there were 8,357 or 55.38 per cent of the 15,090 cases in which a diagnosis or history of a chancre was recorded. The remaining 6,733 case records, or 44.62 per cent gave no indication that either the patient or any physician had recognized a chancre.

Of the total 15,090 case records 9,266 or 61.40 per cent were of male patients, and 5,824 or 38.60 per cent were of females. But among the 9,266 male patients 835 or 8.04 per cent presented chancres on admission, as determined by darkfield examination, while only 136 or 2.33 per cent of the 5,824 female patients presented chancres. There were thus more than three times as many chancres found among the male patients as among the females.

No attempt was made to tabulate facts from the 7,386 case records giving only the history of chancres, due to the probable unreliability of the patients' account of the location, duration, and other facts in which we were interested. The records of 971 cases in which a darkfield diagnosis of primary syphilis was made were analyzed according to sex, age, color, and marital status, the source of infection, the exact location of the lesions, and the duration of the lesions before diagnosis.

As might be expected from the earlier sexual maturation of the female, a larger percentage of girls than of boys were infected in age periods before 21. Males and females together and each separately reached a peak age of infection in the decade 21 to 30, in which age period more than half of all of the patients presenting chancres were found. A more detailed analysis of these figures, however, throws an interesting light on this matter (table 1).

Of the 971 cases 57.8 per cent were white males and 8 per cent were white females, while 28.2 per cent were colored males and 6 per cent were colored females. The analysis of sex, age, and color distribution (chart 1) indicates that white males and females and colored males reached the peak

* Received for publication February 27, 1939.

† With assistance from John L. Gillen, M.D., Clinical Assistant and Marie Di Mario, Statistician, New York City Department of Health.

TABLE I

Number and Percentage of Cases of Each Sex-Race Group in Each Age Group
Age, Sex, and Color

Sex and Color	16—		16-20		21-30		31-40		41-50		50+		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
White—Male	3	.5	49	8.7	258	46.0	151	26.9	83	14.8	17	3.1	561	100.0
White—Female	2	2.6	16	20.5	44	56.4	15	19.2	1	1.3	0	0.0	78	100.0
Colored—Male	1	.4	30	10.9	172	62.8	59	21.5	10	3.7	2	.7	274	100.0
Colored—Female	1	1.7	27	46.6	25	43.1	5	8.6	0	0.0	0	0.0	58	100.0
Total	7	.8	122	12.8	499	51.6	230	23.9	94	9.9	19	1.0	971	100.0

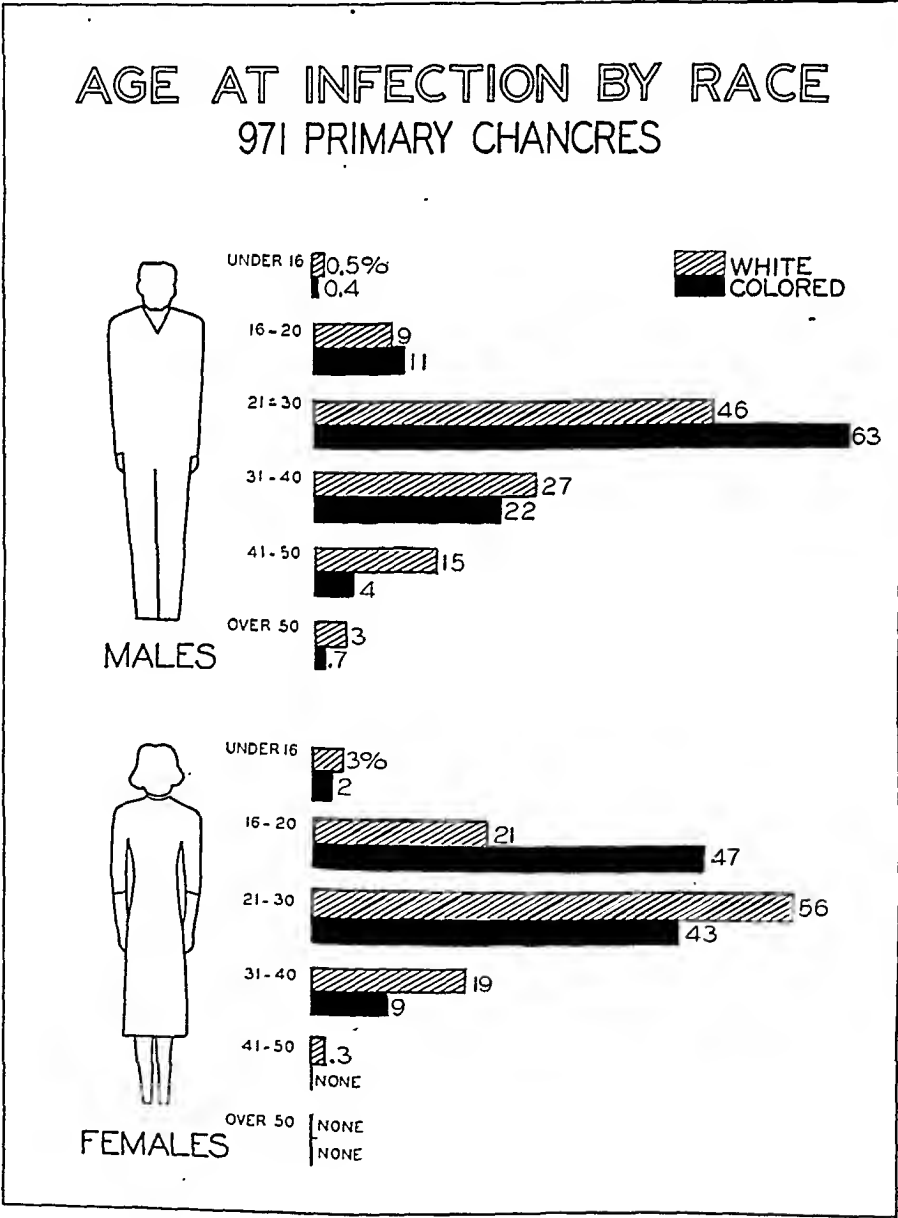


CHART I

age of infection in the 21 to 30 decade. Colored females, however, reached the peak age in the five year period—16 to 20. Of the white females 23.1 per cent were in the age groups below 21, while of the colored females 48.3 per cent were younger than 21 years of age. Colored males also are prone to earlier infection than white males, for 74.1 per cent of colored males as compared with only 55.2 per cent of white males were younger than 31.

Table 2 gives by sex the marital status of the 971 patients presenting chancres on admission. Of the total, nearly one-third were married but 53.7 per cent of the women, and only 26.7 per cent of the men were married, a ratio of 2 to 1.

TABLE II

Marital Status	Male		Female		Total	
	No.	%	No.	%	No.	%
Single.....	577	66.7	50	36.7	607	62.5
Married.....	223	26.7	73	53.7	296	30.5
Other *.....	55	6.6	13	9.6	68	7.0
Total.....	835	100.0	136	100.0	971	100.0

* Divorced; widowed, separated.

When the facts given in table 2 are considered together with table 3 giving the alleged sources of infection, they become especially significant. Our analysis showed that 34.5 per cent of the women, and only 1.4 per cent of the men claim that syphilis had been acquired in marriage. Of the total number of males 78.8 per cent stated that prostitutes were the sources of infection. Among the women 45, or 33.1 per cent, admitted to being prostitutes, and believed that they had been infected in the course of practice of prostitution. The three cases of "assault" mentioned in table 3 were those of young boys, the victims of pederasty.

TABLE III

Source of Infection	Male		Female		Total	
	No.	%	No.	%	No.	%
Marital.....	12	1.4	47	34.5	59	6.1
Friend.....	162	19.4	44	32.4	206	21.2
Prostitute.....	658	78.8			658	67.8
Public *.....			45	33.1	45	4.6
Assault.....	3	.4			3	.3
Total.....	835	100.0	136	100.0	971	100.0

* Admitted "public prostitutes."

As indicated in table 4 below, there were 223 married men of whom only 4.5 per cent claimed a marital source of infection, 37.2 per cent named a friend, and 58.3 per cent attributed infection to prostitutes. (Chart 2.) Of

TABLE IV
Marital Status—Male

Source of Infection	Single		Married		Other *		Total	
	No.	%	No.	%	No.	%	No.	%
Marital.....	—	—	10	4.5	2	3.6	12	1.4
Friend.....	69	12.4	83	37.2	10	18.2	162	19.4
Prostitute.....	485	87.1	130	58.3	43	78.2	658	78.8
Assault.....	3	.5	—	—	—	—	3	0.4
Total.....	557	100.0	223	100.0	55	100.0	835	100.0

Marital Status—Female

Source of Infection	Single		Married		Other		Total	
	No.	%	No.	%	No.	%	No.	%
Marital.....	—	—	43	58.9	4	30.8	47	34.6
Friend.....	23	46.0	16	21.9	5	38.4	44	32.4
Public †.....	27	54.0	14	19.2	4	30.8	45	33.0
Total.....	50	100.0	73	100.0	13	100.0	136	100.0

* Widowed, divorced, separated.

† Admitted "public prostitutes."

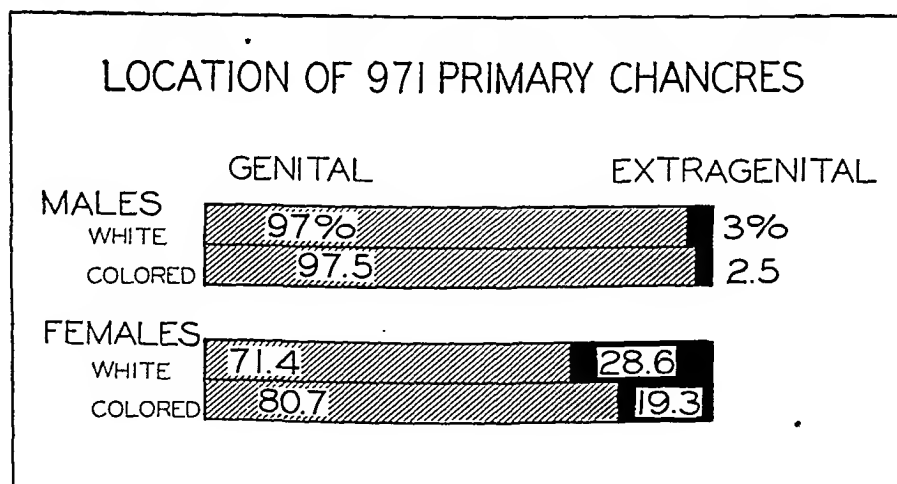
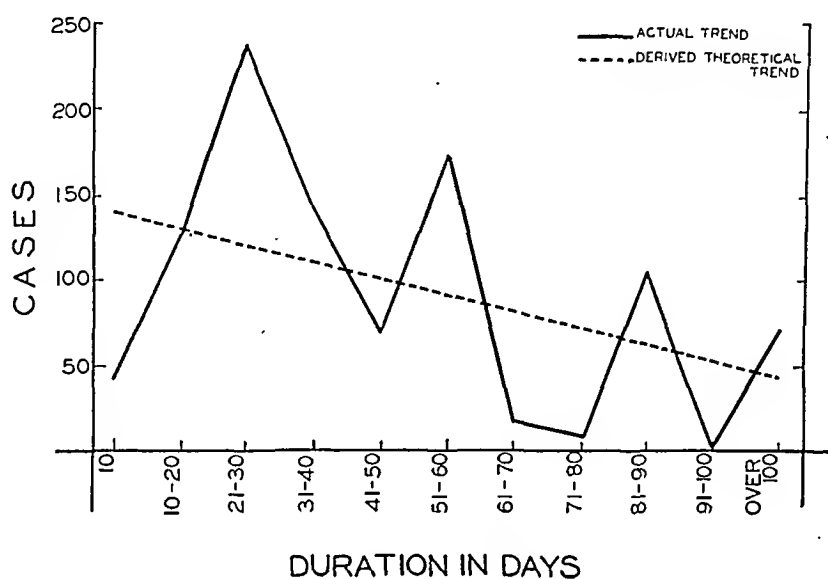


CHART II

557 unmarried males, 87.1 per cent indicated prostitutes, and 12.4 per cent named friends as sources of infection.

One of the most interesting aspects of the study dealt with the anatomic sites of chancres. (Chart 3.) In the total of 971 patients, there were noted

DURATION OF PRIMARY LESION FROM DAY FIRST NOTED BY PATIENT TO DAY OF DIAGNOSIS



Data from New York City Health Department

Chart by American Social Hygiene Association

CHART III

989 chancres, or 18 more chancres than patients. Several patients presented multiple lesions at different anatomic sites. This happened to occur only in male patients, and all were genital chancres. There were, for example, a chancre of the corona together with a chancre of the glans; chancre of the shaft and of the frenum, etc. Table 5 gives the distribution of chancres by sex and color of patients classified as to genital or to extragenital site.

TABLE V
Race, Sex, and Location of Chancres

	Genital		Extragenital		Total	
	No.	%	No.	%	No.	%
White Males.....	555	97.0	17	3.0	572	100.0
Colored Males.....	276	97.5	7	2.5	283	100.0
Total Males.....	831	97.2	24	2.8	855	100.0
White Females.....	55	71.4	22	28.6	77	100.0
Colored Females....	46	80.7	11	19.3	57	100.0
Total Females.....	101	75.4	33	24.6	134 *	100.0

* In two female cases the exact location of the chancre was not given; hence only 134 cases out of 136 were classified.

Several points of interest are brought out in the above table. Of the total 989 chancres, 57 or 5.7 per cent were extragenital. This is in harmony with the results of other similar studies.¹ A second noteworthy point, however, illuminates the first, for it is seen that while extragenital lesions constitute only 2.8 per cent of those found in males, they constitute 24.6 per cent of those in females, and 28.6 per cent in white females, as compared with 19.3 per cent in colored females.

Table 6 gives the location of genital and extragenital chancres in male patients. The commonest site was the corona. Unfortunately, 195 chancres were listed as "penile," which prevented more exact anatomical classification. In males the commonest extragenital site of infection was the lip.

TABLE VI
Males

Location of Chancre	Number
<i>Genital:</i>	
Meatus.....	19
Urethra.....	3
Glans.....	81
Corona.....	228
Frenum.....	33
Prepuce.....	144
Shaft.....	120
Penile scrotum junction.....	2
Scrotum.....	6
Penile.....	195
<i>Total Genital.....</i>	<i>831</i>
<i>Extragenital:</i>	
Finger.....	3
Tonsil.....	3
Chin.....	1
Lip.....	16
Anus.....	1
<i>Total Extragenital.....</i>	<i>24</i>
<i>Total Genital and Extragenital.....</i>	<i>855</i>

The location of chancres in female patients is recorded in table 7. The labia majora was the commonest genital site. It is worthy of note that only five chancres were found on the cervix, which, according to one investigator, is by far the commonest site in the female when thorough examinations are made.²

The lip in the female as in the male was the commonest extragenital site. Of the total of 57 extragenital lesions in male and female patients, no less than 40 were on the lips, a fact which emphasizes the great importance of careful attention to labial and oral lesions.

TABLE VII

Females

Location of Chancre	Number
<i>Genital:</i>	
Cervix.....	5
Labia.....	12
Labia majora.....	47
Labia minora.....	15
Meatus.....	1
Urethra.....	1
Vagina.....	5
Vulva.....	15
<i>Total Genital.....</i>	<i>101</i>
<i>Extragenital:</i>	
Lip.....	24
Palate.....	1
Breast.....	3
Groin.....	1
Thigh.....	3
Anus.....	1
<i>Total Extragenital.....</i>	<i>33</i>
<i>Total Genital and Extragenital.....</i>	<i>134</i>

An analysis of the duration of the primary lesions according to marital status, also by sex, color groupings showed that the largest number of patients came for diagnosis 21 to 30 days after they themselves had recognized a lesion. The next largest number came 51 to 60 days, and the third largest 81 to 90 days after they had noticed a lesion. A graph of these data presents a series of peaks 30 days apart, and the peaks are quite similar for

TABLE VIII
Duration of Lesion and Marital Status

Duration (Days)	Single		Married		Other		Total	
	No.	%	No.	%	No.	%	No.	%
10-	20	3.3	6	2.0	2	2.9	28	2.9
10-20	77	12.8	44	14.8	8	11.7	129	13.4
21-30	138	22.9	75	25.4	25	36.3	238	24.6
31-40	95	15.9	36	12.2	11	16.0	142	14.8
41-50	41	6.8	18	6.1	5	7.2	64	6.6
51-60	112	18.7	51	17.2	5	7.2	168	17.3
61-70	10	1.6	6	2.0	1	1.4	17	1.8
71-80	10	1.6	0	0	0	0	10	1.0
81-90	63	10.6	32	10.8	9	13.0	104	10.8
91-100	0	0	0	0	0	0	0	0
100+	35	5.8	28	9.5	3	4.3	66	6.8
Total	601	100.0	296	100.0	69	100.0	966	100.0

both sexes, both white and colored and for single and married patients. (Chart 4.) Only 28 (3 per cent) out of 966 chancres for which the duration was given came to attention within the first 10 days after their appearance, and 571 (59 per cent) out of the 966 continued untreated for more

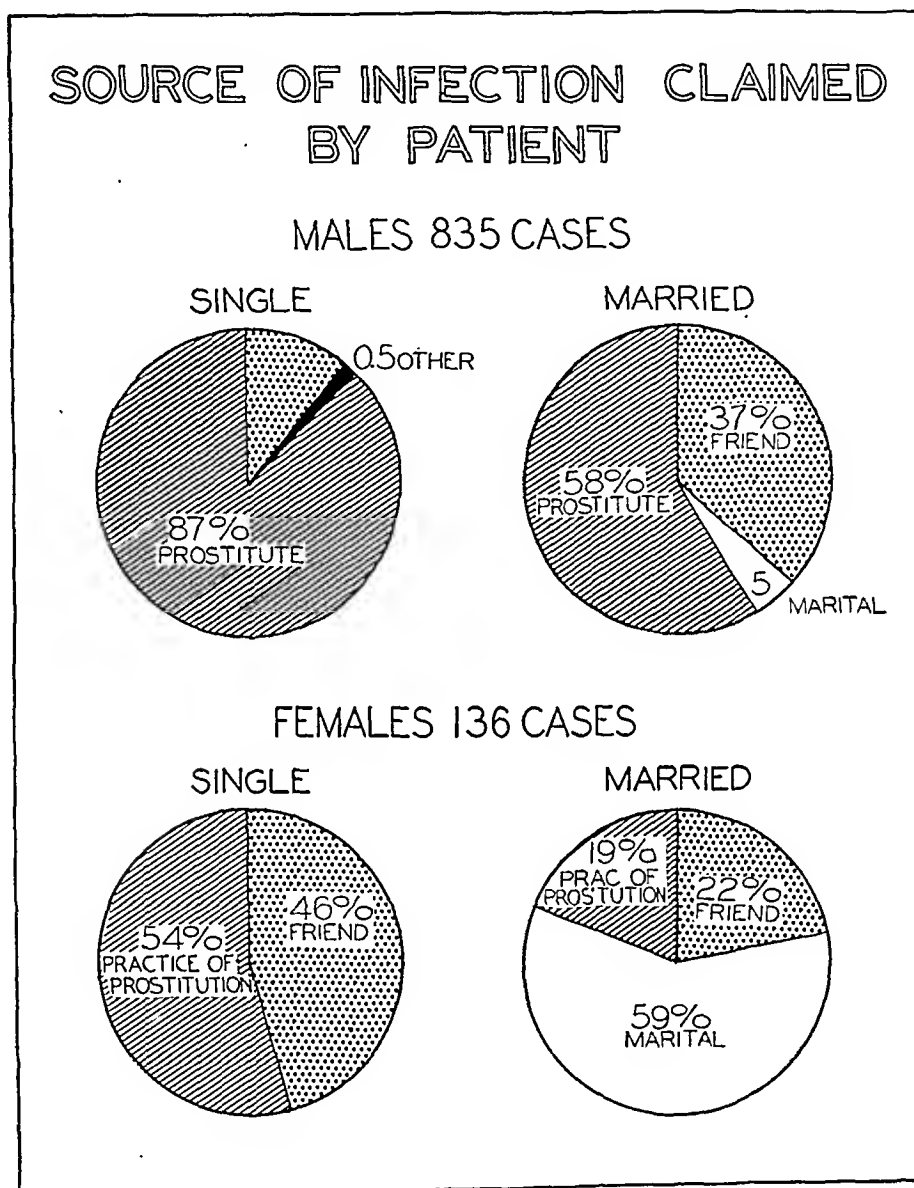


CHART IV

than 30 days after the "sore" had been noticed. In 66 (7 per cent) instances chancres persisted without treatment for more than 100 days. In some of these cases there were mixed infections, others were discovered only after the secondary rash had appeared, leading the patient to seek medical attention.

COMMENT

In the modern program for combating syphilis, nothing is more important than finding the cases of syphilis early, and bringing them under the treatment which can make them non-infectious. The best interest of the patient and of the public requires that syphilis come under treatment in the chancre stage. How to assure that patients will suspect syphilis, or at least some serious condition, when a chancre exists, is a difficult problem in health education, especially when it is recognized that many primary lesions are inconspicuous, mild, or atypical manifestations of syphilis, that they may appear anywhere on the body surface, except the teeth and the nails, and disappear without treatment. When physicians not infrequently fail to suspect a lesion of being actually a chancre, how can we teach lay people to take "cold sores," "pimples," "canker sores," "fever blisters" and "hair cuts" to a doctor for a darkfield examination?

The contrast between the number of diagnosed cases of chancre in men and women is striking. This is probably because the chancre in the female is so often hidden away out of the sight of the patient. She sees and suspects nothing, and therefore does not visit a physician. By what process of health education can a woman be made to suspect the presence of a chancre of the cervix, which may be one of the commonest sites of infection in the female?

In order to encourage people to suspect lesions that may be of serious import, and, therefore, to take them to physicians for darkfield examinations, we should teach the public that every lesion of the skin or mucous membrane, however simple, that does not heal within one week should be shown to a physician. Equally we must advise every physician to perform darkfield examinations on every lesion not easily explained, if that lesion has persisted for more than one week. Lesions appearing 10 days to 10 weeks after unaccustomed intimate contacts, such as sexual relations or kissing, should be especially suspected. Physicians should be warned not to trust solely in a clinical diagnosis of lesions of the skin and mucous membrane, but to use the darkfield microscope, not once, but repeatedly, at the same time following the course of such lesions with serologic tests. The common error of ruling out the possibilities of a chancre because the Wassermann or Kahn test is negative should be corrected. The equally frequent blunder of applying an antiseptic dressing to a suspicious lesion should be rectified in practice.

The proper procedure for a physician, upon finding a lesion which has not healed in one week and for which there is no obvious explanation, is as follows:

- (1) Take a careful history of contacts.
- (2) Make a clinical examination, including an examination of the lymphatic chain draining the site of the lesion, noting any adenopathy.
- (3) Make careful darkfield microscopic examinations of serum expressed from the lesion, and, if necessary, of fluid from neighboring enlarged lymphatic glands.

- (4) If the darkfield examinations are negative, apply to the lesion only a simple saline dressing.
- (5) Take a specimen of blood for serologic tests for syphilis.
- (6) Instruct the patient to return for a repetition of the examination in two days, and warn him or her of the danger of transmitting infection to others.
- (7) Repeat this procedure as often as necessary to rule out or to diagnose syphilis.

Physicians in every branch of practice should know and follow substantially these procedures. A chancre of the eyelid has been missed by an ophthalmologist. Chancres of the tonsils have been wrongly diagnosed by otolaryngologists. Chancres of the anus, breast, finger, lip, thigh, axilla and scalp have been missed by specialists and general practitioners, to the disadvantage of the patients and the public health and the discredit of the medical profession.

It is not believed that extragenital lesions of syphilis are actually commoner in females than in males, as our figures seem to indicate. The apparently higher comparative frequency of extragenital lesions in women is due to the fact that the genital lesions of syphilis, especially chancres of the cervix, were often overlooked by female patients and by physicians also in some cases.

The importance of correctly diagnosing extragenital chancres can hardly be overestimated. In all probability the extragenital lesion is even more dangerous than the genital lesion, because the patient does not suspect a "venereal disease," and because the disease may spread by kissing, and conceivably also by the use of cups, glasses and pipes, in the case of the lip and buccal cavity chancres. Chancres of the fingers are not very uncommon, and can be the means of the transmission of the disease.

It is noted above that negro youths are subject to earlier infection than white youths. This tendency arises out of the poverty, overcrowding, lack of educational opportunity, and generally low cultural level at which a large part of the colored population of New York City is obliged to live. It may also be that the alleged earlier sexual maturation of negro boys and girls plays an important part in the somewhat earlier age of infection.

The high incidence of infection in the age groups below 31 should receive attention from the medical profession and health authorities. More than 64 per cent of the chancres diagnosed in this group were found in young people under 31 years of age.

The findings of this study with reference to marital infections is in accord with general clinic experience. A much larger proportion of female than of male patients are victims of marital syphilis, while many more men are single than are married at the time of infection. However, men, whether married or single, are infected by prostitutes (at least according to their own statements) in the largest percentage of cases.

All of this serves to emphasize the great importance of prostitutes as spreaders of syphilis, and the need to deal with the prostitution racket, not only for the benefit of law and order, but also in the vital interest of health protection. In this connection it is interesting to note that of more than 3800 women arrested and charged with sex offenses, usually prostitution, and examined by the Department of Health in our diagnostic clinics, 58 per cent were found to have syphilis or gonorrhea, or both. No practical method had been found for protecting the public from the spread of syphilis by prostitutes other than by reducing commercialized prostitution to its minimum through the application of police measures.

As to marital infections, the operation of the new law in New York City requiring a medical and serological examination prior to marriage may prevent the transmission of syphilis in the marriage relationship in a considerable number of cases.

The duration of the chancres prior to diagnosis is worthy of attention, because the patient, in ignorance of the nature of the lesion, may spread the disease to others. It is appalling to consider that only 28 out of 966 chancres came to medical attention within 10 days after their appearance, and that far more than half of all the chancres continued undiagnosed more than 30 days after they had first been noticed by the patients. Here again we have a clear indication for more intensive educational procedures directed to the task of bringing the early lesions of syphilis promptly to medical attention.

SUMMARY

A study of 15,090 syphilis case records in the New York City Department of Health syphilis clinics, revealed 971 cases of syphilis diagnosed in the chancre stage. These case records were analyzed according to sex, age, color and marital status, and classified according to source of infection, site of lesion, and duration of lesion prior to diagnosis. Of the total 15,090 cases, 6.4 per cent were diagnosed in the chancre stage and an additional 48.9 per cent gave a definite history of a primary lesion. Thus there is a history or definite diagnosis of a chancre in more than half of the 15,090 cases.

In white males and females and in colored males, the peak age of infection was in the 21 to 30 age period. Colored girls, however, are infected earlier, the peak being in the 16 to 20 age period. Nearly 25 times as many women as men claim marital sources of infection. More than three-fourths of all the males named prostitutes as sources of infection, but 31 per cent more single than married men attributed infection to prostitutes.

Of all the chancres definitely diagnosed, 5.7 per cent were extragenital, but because genital chancres are often missed in females, the ratio of extragenital to genital chancres was eight times as high in females as in males. The lips are by far the most common sight of extragenital chancres. Of the 971 cases diagnosed in the primary stage, only 3 per cent sought medical

attention within 10 days after first noticing a lesion. Over half waited more than 30 days and 7 per cent delayed for over 100 days, after noticing a "sore" before asking a physician to make a diagnosis.

The facts revealed in this study are briefly discussed from the point of view of the public health problems involved.

REFERENCES

1. (a) HAZEN, H. M.: Syphilis, 1928, C. V. Mosby Co., St. Louis, pages 35 and 78.
(b) ORMSBY, O. S.: Diseases of the skin, 1937, Lea and Febiger, Philadelphia, page 813.
(c) WAGENER, F.: Extragenitale syphilitische Primäraffekts an der Bonner Hautklinik seit 1924, Inaug. Dissert., Bonn, 1935.
(d) SZEWAHOWSKI, P.: The localization of the syphilitic chancre, Ann. d. mal. ven., Paris, 1935, xxx, 43.
2. DAVIES, T. A.: Primary syphilis in the female, 1931, Oxford Publication, page 10. (Out of 584 primary chancres in women Dr. Davies found 256 or 44.0 per cent on the cervix.)

CLINICAL STUDIES IN ACIDOSIS AND ALKALOSIS; USE AND ABUSE OF ALKALI IN STATES OF BICARBONATE DEFICIENCY DUE TO RENAL ACIDOSIS AND SULF- ANILAMIDE ALKALOSIS *

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For quite some time we have been impressed with the value of alkali administration in the form of sodium *r*-lactate, not only as an emergency measure in relieving acutely developing acidosis in subjects with severe diarrhea, uncontrolled diabetes, or severe renal insufficiency, but also as a means of preventing the development or recurrence of severe acidosis in patients with renal defects not so severe as to be otherwise incompatible with fairly normal life. The purpose of this paper is threefold: (1) To review experiences with some patients in whom the renal lesion progressed to a fatal degree and to point out how acidosis may on the one hand develop quite insidiously and not be recognized unless looked for, or on the other hand, develop to an extreme degree quite suddenly, just as it does in diabetics or following severe diarrhea and dehydration; (2) to report findings in an infant whose only serious renal defect at this time seems to be inability of the tubules to reabsorb BHCO_3 , and who requires an extraordinary amount of potential alkali daily to keep from developing severe and perhaps fatal acidosis; and (3) to discuss similarities and differences between such states of BHCO_3 deficiency and the condition brought about by sulfanilamide administration, which primarily is a carbon dioxide deficit type of alkalosis, and not acidosis, as generally stated.

The first case to be reviewed is that of Robert D., a boy previously reported while still living by Schoenthal and Burpee¹ as a case of renal rickets and infantilism. Although born with polycystic kidneys (figure 1) and undoubtedly suffering from considerable renal insufficiency from birth as a result, he nevertheless lived to be nine years old. For many years acute illnesses, attended usually by diminished food and fluid intake and occasionally by excessive water and electrolyte loss because of fever and vomiting, would be followed by rather marked changes in the electrolyte pattern of his blood plasma.¹ Frequently acidosis would develop to such a degree as to make treatment an emergency. Sodium bicarbonate was used as sodium *r*-lactate therapy had not yet been developed. Relief of acidosis at various times seemed to have been a life-saving measure. BHCO_3 and pH data plotted on the Hastings chart² designed with the use of triangular co-ordinate paper to indicate the acid base balance, indicate clearly that during

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FIG. 1. The larger kidney, which is of approximately normal size, is a mass of cysts and its ureter is without a patent lumen; it was, therefore, entirely without function. The smaller kidney measures $4 \times 2 \times 1.5$ cm., and is approximately the size of the kidney of a premature infant of seven months' gestation. It contains many small cysts and much fibrous tissue.

the periods of bicarbonate deficit the acid base balance has been shifted into the zone characteristic of acid excess or alkali deficit and that the intra-venous administration of a sufficient amount of sodium bicarbonate restores the acid base balance approximately to a normal position (figures 2 and 3). In this patient the cause of the bicarbonate deficit seemed largely the result of primary urinary loss of BHCO_3 , although some reduction was probably also accounted for by increase in phosphoric and sulphuric acid. In figure 4 positions in the acid base chart of three other cases of renal insufficiency are plotted and indicate clearly that acidosis may exist in the absence of phosphate retention, presumably because of a diminished ability of the kid-

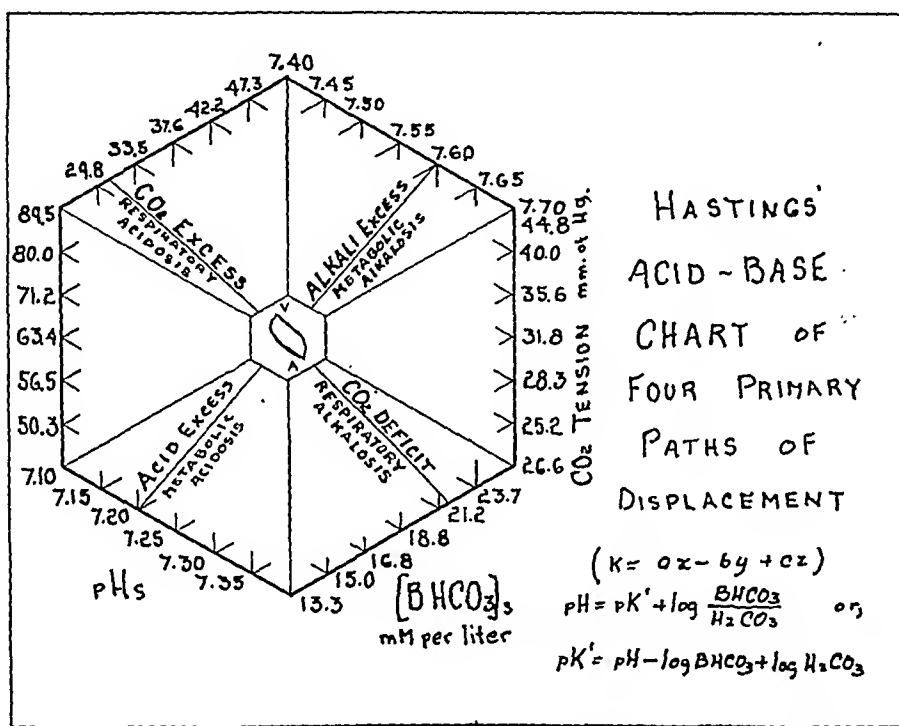


FIG. 2. The Hastings acid base balance chart, showing the four primary paths of displacement.

neys to excrete fixed acid neutralized by ammonia and because of failure to secrete urine of maximal acidity. Such failure leads to loss of BHCO_3 by way of the urine, and a new plasma electrolyte pattern develops which is characterized chiefly by diminished BHCO_3 concentration and an increased BCl concentration. In other words, the intake of food and water provides sufficient chloride and water to permit normal or excessive retention of sodium chloride and water despite polyuria, but the "alkali ash" content of the food, because of the renal insufficiency, becomes inadequate for the maintenance of a normal BHCO_3 content.

The second case is that of David A., a boy of five years, with glomerular nephritis and with somewhat more rapid loss of renal function than occurred

in Robert D., and in whom acidosis once developed very suddenly and to a severe degree after what seemed to have been a trivial illness characterized by loss of appetite and diminished fluid intake which lasted but a few days. His clinical appearance resembled very much that of diabetic coma. From figure 5 it may be noted that by the time the attack of acidosis developed there had been a gradual diminution in the ability of his kidneys to clear urea from the blood, maximum urea clearance values having dropped from 42 per cent of the normal to 11 per cent. Inorganic phosphate, however, had not yet increased to an abnormal concentration. The usual therapeutic dose of

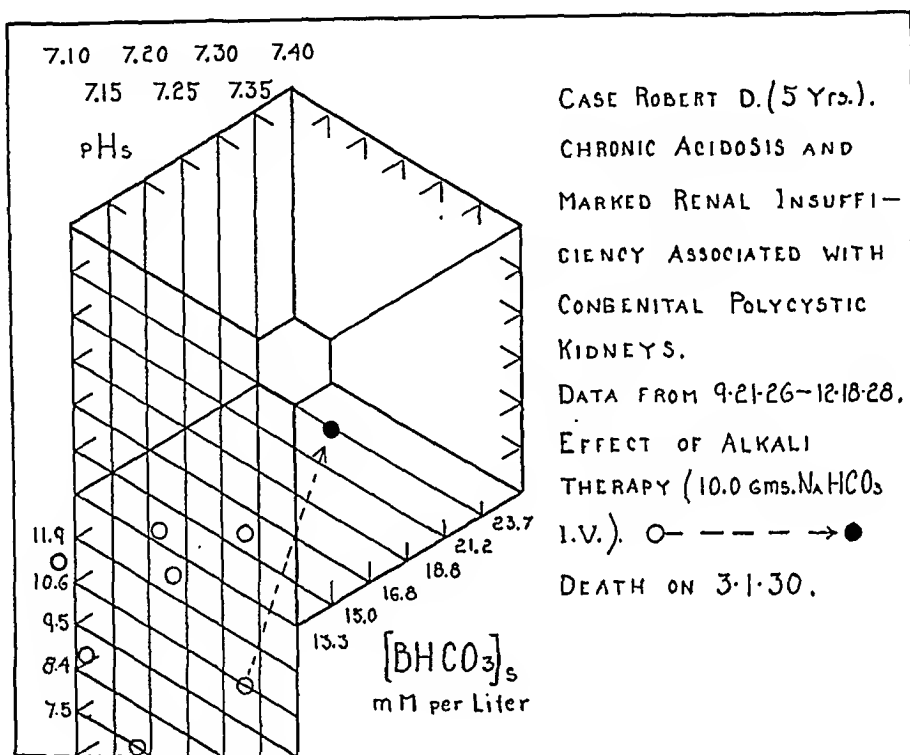


FIG. 3. Serum BHCO_3 and pH values of case Robert D. (severe renal insufficiency) fall always in the zone of acid excess or alkali deficit (metabolic acidosis).

sodium *r*-lactate, 60 c.c. of one-sixth molar solution per kilogram of body weight, was sufficient to relieve the BHCO_3 deficit completely, but without the continued administration thereafter of sodium lactate, acidosis recurred. It was then relieved and its recurrence prevented by the daily administration of 5 c.c. of molar sodium *r*-lactate per kilogram of body weight daily, approximately 1 c.c. per kilogram being administered in milk or other fluids five times daily. This patient lived for more than a year after the development of severe acidosis, and it seems very likely that the continued administration of sodium lactate, by preventing recurrence of severe acidosis, played a large part in prolonging his life to this extent.

The third case is that of Beverly R., also with glomerular nephritis but with still more rapid loss of renal function, in whom sodium *r*-lactate admini-

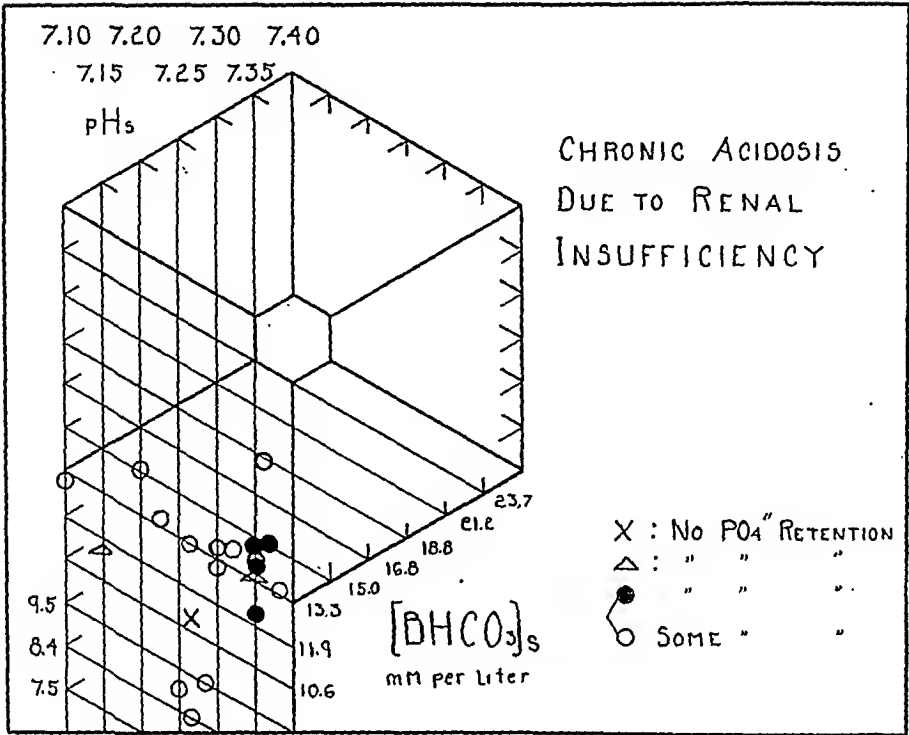


FIG. 4. Serum BHCO₃ and pH values of three cases of renal insufficiency with little or no phosphate retention, demonstrating clearly the existence of acidosis of the metabolic type.

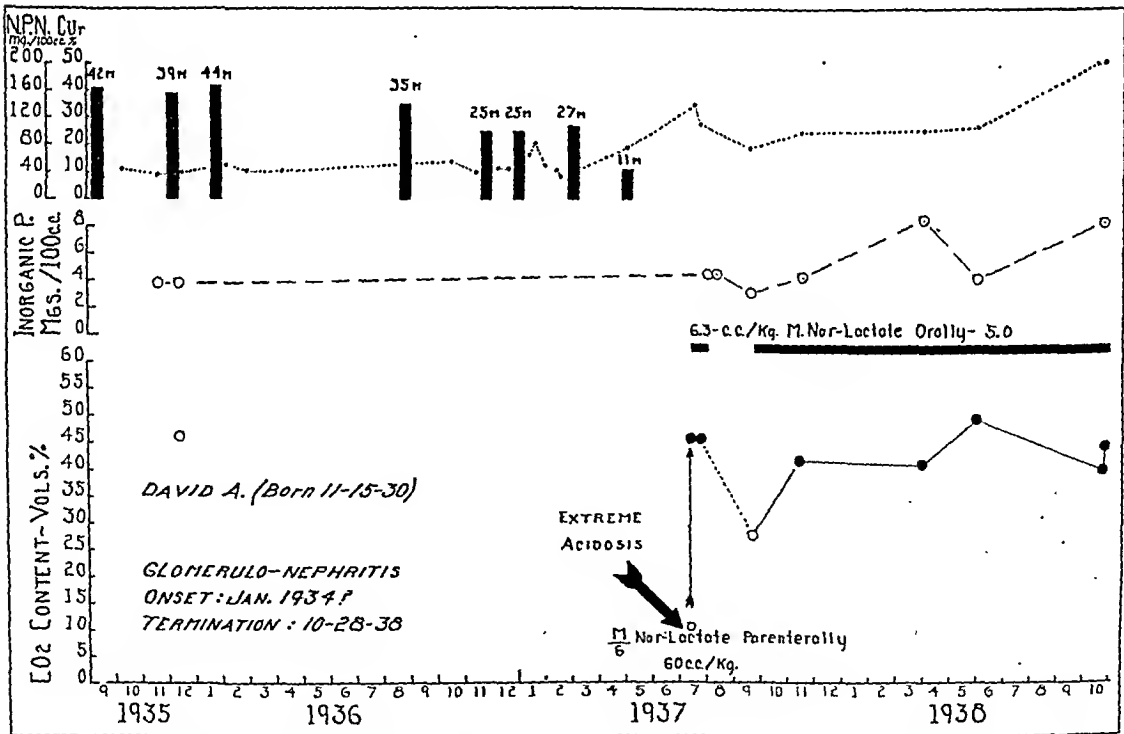


FIG. 5. Relationship between diminishing urea clearance ability, rising plasma N.P.N., and inorganic phosphate and development of acidosis in case David A., with glomerulo-nephritis.

istration was also necessary both as an emergency measure in the treatment, and also as a means of preventing acidosis. Figure 6 indicates that two severe attacks of acidosis developed at a time when her renal function as judged by urea clearance tests was still fairly good (more than 40 per cent of the normal). The inability of the salts of Ringer's solution or of dextrose to relieve such attacks of acidosis compared with the effectiveness of sodium *r*-lactate is clearly demonstrated in table 1. As in the previous case, David A., the attacks of acidosis in this case also occurred in the absence of phosphate retention and similarly acidosis again developed later when preventive

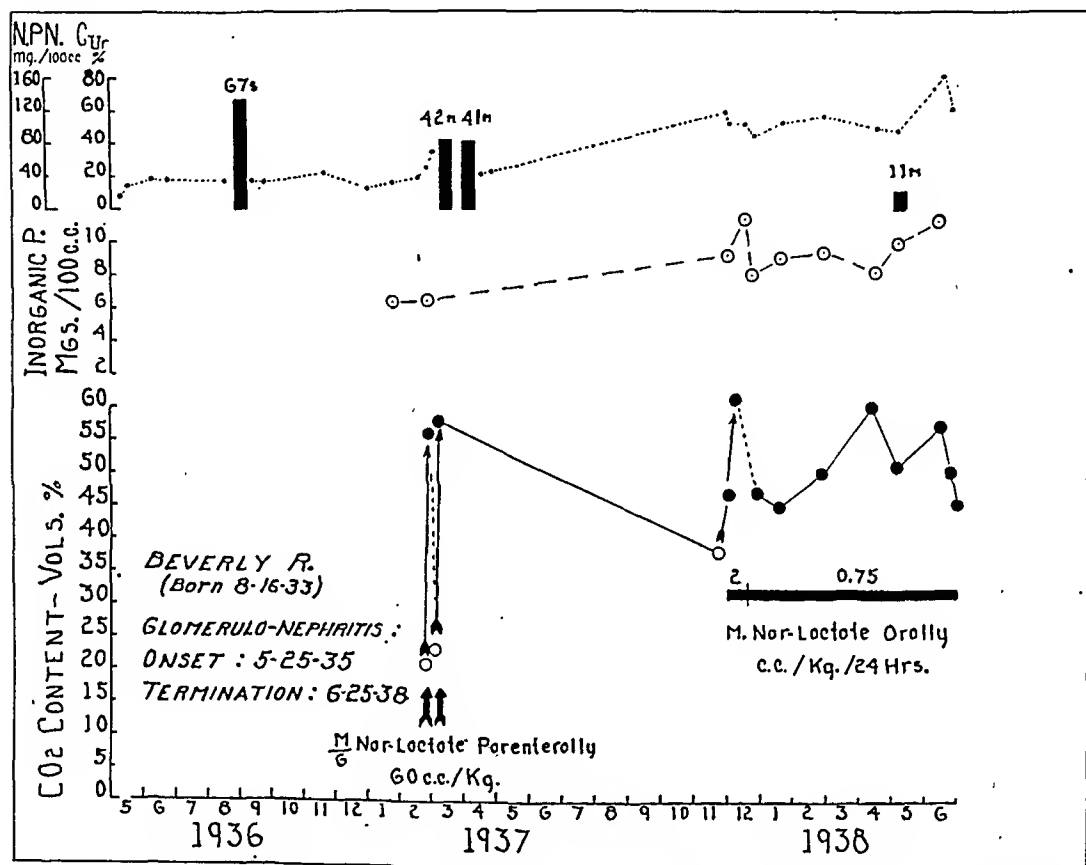


FIG. 6. Relationship between diminishing urea clearance ability, rising plasma N.P.N., and inorganic phosphate and development of acidosis in case Beverly R., with glomerulo-nephritis.

measures were not instituted. Later the continued tendency for the development of acidosis was effectively overcome by the daily oral administration of sodium *r*-lactate. In this case a rather small amount proved effectual (0.75 c.c. of molar sodium *r*-lactate per kilogram per day). This patient also lived more than a year following the development of severe acidosis, and as renal impairment increased to a greater degree, phosphate retention finally made its appearance.

In the cases cited above, BHCO_3 deficit was but one manifestation of generalized renal insufficiency and relief of acidosis with sodium lactate

TABLE I
Effects of (1) Dextrose, (2) Ringer's Solution, and (3) Sodium Lactate in Relieving Acidosis in a Case of Chronic Active Hemorrhagic Nephritis

Period	Date	Time	Blood Serum								
			CO ₂ Cont. Vols. %	NaCl Mg. %	N.P.N. Mg. %	Na mM	Prot. Gm. %	Alb. Gm. %	Glob. Gm. %	Ca Mg. %	Inorg. P. Mg. %
Before 14 hours after 150 c.c. molar Na r-lactate + 750 c.c. Ringer's solution + 150 c.c. 10% dextrose I.V. and Subcut.	2-25-37 2-26-37	7:45 p.m. 10:00 a.m.	21.0 55.9	— 634	56.2 48.5	—	3.93	1.00	2.93	6.6	6.5
		Expected Difference	(62.5) -6.6								
Before 6½ hours after 150 c.c. 20% dextrose I.V. (40 c.c. isotonic/Kg. B. wt.)	3-1-37 3-1-37	9:15 a.m. 3:45 p.m.	23.3 26.2	644	70.9	133.4					
		Expected	?								
Before 18 hours after 780 c.c. Ringer's solution Subcut. (38.7 c.c. isotonic or 6.67 M.Eq.B+/Kg.B.wt.)	3-1-37 3-2-37	3:45 p.m. 9:40 a.m.	26.2 31.0	644 634	60.0	135.4					
		Expected	?								
Before 6 hours after 780 c.c. 1/6 molar Na r-lactate I.V. and Subcut. (36.7 c.c. "isotonic" or 6.67 M.Eq.B+/Kg.B.wt.)	3-2-37 3-2-37	9:40 a.m. 3:30 p.m.	31.0 58.2	634 595	60.0	135.4 139.7					
		Expected Difference	(64.5) -6.3								

Case B.R. No. M-830
Age = 3½ yrs.
Wt. = 12.2 — 13.2 Kg.
Duration of Nephritis 2 yrs.
Type: "Nephrotic"

Urea clearance { 9-2-36 Cs = 67%
 3-10-37 Cm. = 42%
Acidosis developed during period of acute
infection associated with fever, vomiting,
diarrhea, and oliguria, all of which had
ceased before this period of study.

Urinary Output (24 hrs.)
2-23-37 = 1002 c.c.
2-24-37 = 770 c.c.
2-25-37 = 260 c.c. (onset of infection)
2-26-37 = 286 c.c.
2-27-37 = 571 c.c.
2-28-37 = 678 c.c. (no fever)
3- 1-37 = 885 c.c.
3- 2-37 = 1022 c.c.

Case B.R. No. M-830
Age = 3½ yrs.
Wt. = 12.2 - 13.2 Kg.
Duration of Nephritis 2 yrs.
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Urea clearance { 9-2-36 Cs = 67%
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2-27-37 = 571 c.c.
2-28-37 = 678 c.c. (no fever)
3- 1-37 = 885 c.c.
3- 2-37 = 1022 c.c.

provided only a partial cure. In the following case a very unusual situation, in fact one that apparently has not previously been described, was encountered, namely, a persistent excretion of BHCO_3 into the urine as the only clearly evident expression of renal insufficiency which led to chronic severe acidosis and which necessitated the continued oral administration of relatively enormous doses of alkali. Such alkali administration, however, seems thus far to have compensated completely for the renal defect. This patient, Robert G., was an infant of four months when first seen by us. His his-

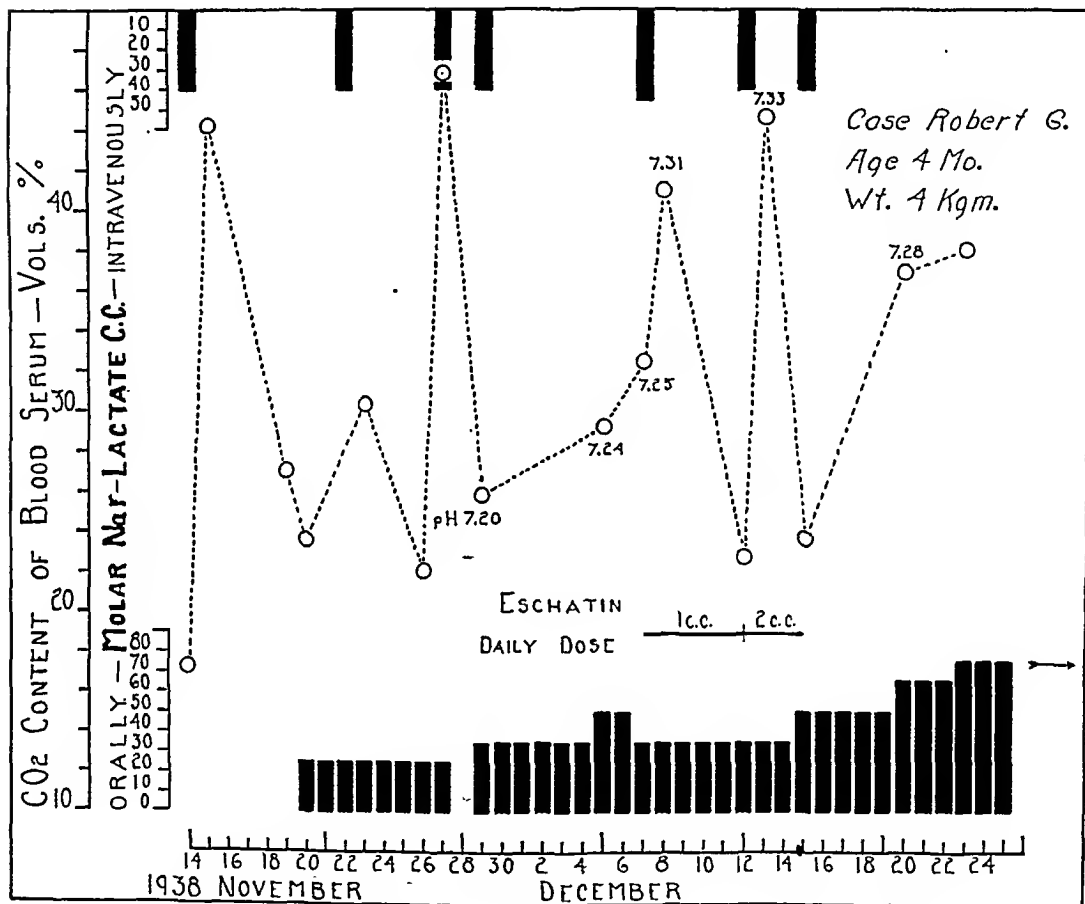


FIG. 7. Gradual control of the acidosis of Robert G. with increasing amounts of orally administered sodium *r*-lactate supplemented with its parenteral administration whenever necessary.

tory was that he had had a normal birth and apparently had developed quite normally for the first two months of his life and then began to become less active, to lose his appetite, and to have bouts of vomiting, sometimes accompanied by dyspnea. After one such bout he was admitted to the St. Louis Children's Hospital with the typical picture of severe acidosis requiring immediate treatment. This treatment was instituted in the form of parenterally administered sodium *r*-lactate and was effectual (figure 7). At first no satisfactory reason for the development of such severe acidosis was discovered. With its recurrence later, however, a study of the urine and

renal function was made and the cause was determined as may be seen from table 2. The urine continued to be voided with a pH approximately that of blood, despite the fact that the loss of BHCO_3 into the urine would lead to

TABLE II
Data Relating to pH of Urine in Case Robert G.

Date	Time	Plasma		Urine pH
		CO ₂ Cont. Vols. %	pH	
11-19-38		27.0	—	7.3±
11-23-38		30.5	—	7.2±
11-29-38	12:08 p.m.	25.9.	7.20	7.20
	12:15 p.m.			7.25
	1:10 p.m.			7.26
	2:35 p.m.			7.38
	4:20 p.m.			7.25

severe acidosis. By the use of Hastings' acid base balance chart (figure 8) it may be noted that the blood samples during periods of no treatment or undertreatment were characteristically in the zone of acid excess or BHCO_3

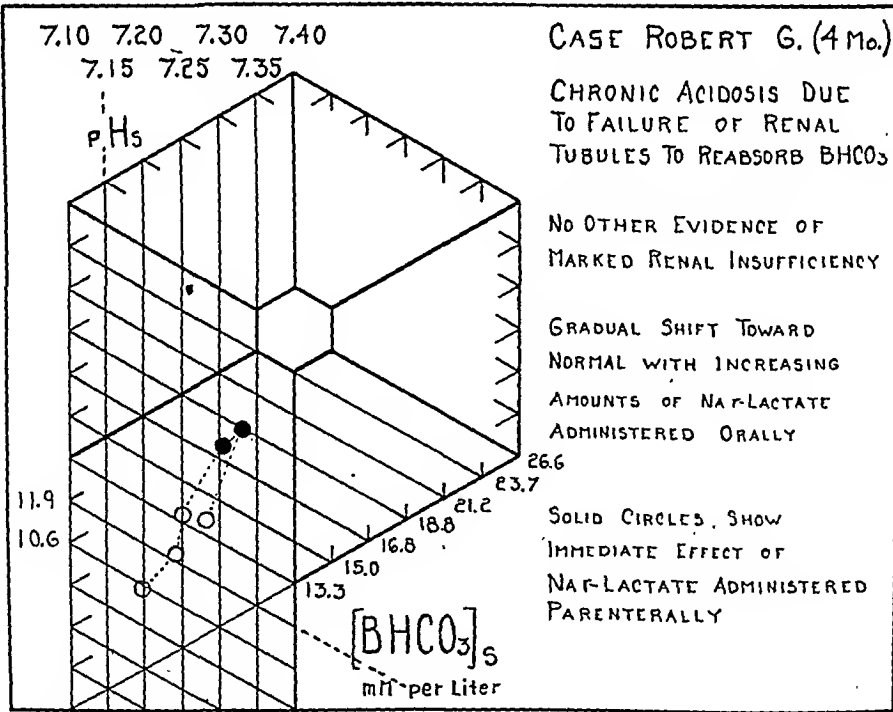


FIG. 8. Serum BHCO_3 and pH values in Robert G., showing BHCO_3 deficit acidosis which was found to be due to continued secretion of alkaline urine.

deficit acidosis, and that treatment with sodium γ -lactate tended to restore them to a position more nearly normal, with, however, always a tendency for reversion to an abnormal position. In table 3 data relative to other phases of renal function are included and indicate that there was a fairly normal ability to clear blood of urea and to excrete phenolsulfonephthalein. Occasionally a trace of albumin was found in the urine, but no evidence of nephritis. At the time of this writing we have word that this child is continuing to look and behave like a normal infant on a normal diet supplemented with 75 c.c. of molar sodium γ -lactate daily. At the time that this

TABLE III
Data Relating to Renal Function in Case Robert G.

Date	Plasma N.P.N. Mg./100 c.c.	Urine					Blood Urea N Mg./100 c.c.	Standard Urea Clearance %
		P.S.P. % Output (min.)	Period Min.	Vol. c.c.	Specific Gravity	Urea N* Mg./100 c.c.		
11-15-38	31.0							
11-21	26.0		991	169	1.016	329	11.7	55
11-22							8.8	72
11-23			1413	365	1.015	344	{ 11.7 (?) 8.8 (?)	68
11-29	34.6				Body Surface Area = 0.268 Sq. M. $10.3 \times (\sqrt[3]{Wt.^2})$			94
12-21		60 (92)						
12-22		55 (112)						

* Urea + Ammonia N by Hypobromite Method.

treatment was first found necessary, the dose amounted to almost 20 c.c. per kilogram of molar solution daily, which is a relatively enormous dose of alkali (figure 7)*

* During the interim between the original writing of this paper and the submission of proof, there occurred some very interesting developments in this infant. Through a misunderstanding, after the infant was discharged from the hospital late in December 1938, he was given only 15 c.c. of molar sodium γ -lactate daily, instead of that amount five times daily. He soon developed clinical signs of severe acidosis again and had again to be treated as an emergency with parenterally administered lactate by Dr. Eugene J. Schwartz of Springfield, Mo., to whom we are indebted for the referral of this most interesting case. On 75 c.c. of molar sodium γ -lactate daily he then continued to do well. In April 1939 the dosage was reduced to 30 c.c. daily, and he still continued to do well. Still on this reduced dosage, he was readmitted to the St. Louis Children's Hospital for study in June 1939, when 11 months of age. His serum carbon dioxide content was 43.9 volumes per cent and pH 7.35, the urine pH still being approximately that of blood. When, however, sodium lactate administration was discontinued, the urine pH dropped and values as low as 5.39 were sometimes noted. The serum pH remained between 7.33 and 7.38 and the carbon dioxide contents remained a little low, between 43.6 and 46.0 volumes per cent, sodium chloride being a little elevated. Recheck of renal function showed qualitatively normal urine, normal blood non-protein nitrogen, 80 per cent excretion of P.S.P. in 61 minutes, and a 24 hour urea clearance value of 85 per cent. When last heard from early in November 1939, he seemed normal in all respects on a normal diet without sodium lactate addition. The tubular lesion, whatever it was, therefore, no longer exists and the infant should continue to do well.

The data secured in the cases mentioned above must be interpreted as indicating that renal lesions may be encountered either in the presence or absence of other manifestations of renal insufficiency which lead to BHCO_3 deficit in the body fluids. Clinical symptoms and findings are those of acidosis, and blood pH and BHCO_3 concentrations when plotted on the Hastings triangular coördinate chart fall in the area characteristic of metabolic acidosis. Restoration of body fluid BHCO_3 may sometimes be necessary as an emergency measure. For such a purpose and also as a preventative, sodium r-lactate administered either parenterally or enterally has been found to be both useful and practical, and represents a logical use of alkali in states of BHCO_3 deficiency.

EFFECTS OF SULFANILAMIDE ON ACID BASE BALANCE

In previous communications from this laboratory,^{3, 4} mention was made of the fact that almost invariably the effect of sulfanilamide on the acid base balance has been misinterpreted. Such workers, for instance, as Southworth,⁵ Long and Bliss,⁶ and Brown and Bannick,⁷ have not only been misled into believing that the hyperpnea which frequently follows sulfanilamide administration is an expression of acidosis which sometimes may require alkali treatment, but these workers have also advocated the illogical use of the administration of sodium bicarbonate with sulfanilamide to prevent acidosis. As mentioned previously, we were struck almost immediately by the disproportion between the relatively marked hyperpnea and the relatively slight reduction in bicarbonate concentrations of the plasma which accompanied such hyperpnea. Our suspicion that these slightly reduced bicarbonate concentrations did not really mean acidosis was first further strengthened by the demonstration that they were usually accompanied by excretion of alkaline urine, and later proved by the demonstration of abnormally alkaline pH values of the blood plasma occurring shortly after sulfanilamide administration. The sequence of events leading to the carbon dioxide deficit type of alkalosis is pictured in figure 9, and is as follows: (1) Primary hyperventilation with blowing off of H_2CO_3 and rise in plasma pH; (2) compensatory excretion of BHCO_3 into the urine, leading both to increase in pH and BHCO_3 of the urine, and diminution in BHCO_3 in the plasma. This fall in plasma BHCO_3 must be considered compensatory and necessary for the restoration of a normal plasma pH. When this has been accomplished, excessive excretion of BHCO_3 into the urine ceases and the reaction of the urine may again become acid. The effect of sulfanilamide on the acid base balance is especially well pictured by the use of the Hastings chart. Figure 10 shows the effect in two normal subjects of a single dose of sulfanilamide equal to 0.2 gram per kilogram of body weight. Figure 11 shows the effect of a comparable dose in two patients. Figure 12 shows more marked displacement into the area characteristic of carbon dioxide deficit alkalosis in two patients not followed from the beginning of

sulfanilamide administration, who continued to receive unusually large doses of the drug. Marshall's⁸ suggested explanation that sulfanilamide may in some manner cause the renal tubules to lose their ability to reabsorb BHCO_3 seems untenable from the experiment previously recorded.⁴ In this experiment a normal subject first took ammonium chloride to produce the acid excess type of acidosis, which was compensated for by complete tubular

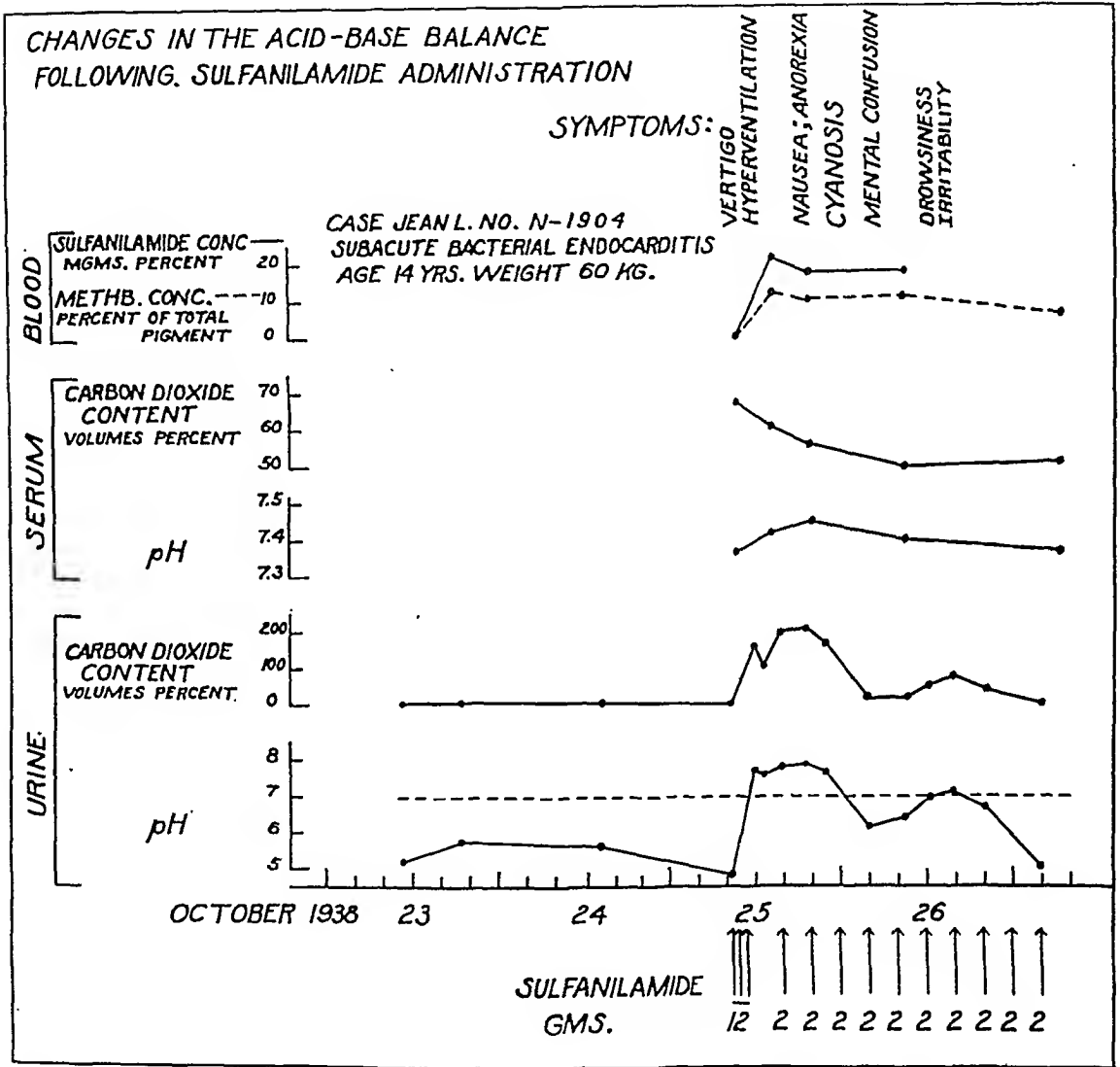


FIG. 9. Effects of sulfanilamide administration on pH and BHCO_3 of the blood and urine.

reabsorption of BHCO_3 . Sulfanilamide was then administered but not followed by the excretion of alkaline urine, which must be taken to indicate that the tubules were capable of reabsorbing BHCO_3 when changes in the acid base balance of the body fluids would demand such reabsorption (figure 13). Coggeshall and Bauer⁹ have reported findings quite similar to ours.

The data presented above indicate clearly that the effect of sulfanilamide is the production of a carbon dioxide deficit alkalosis. There is, therefore,

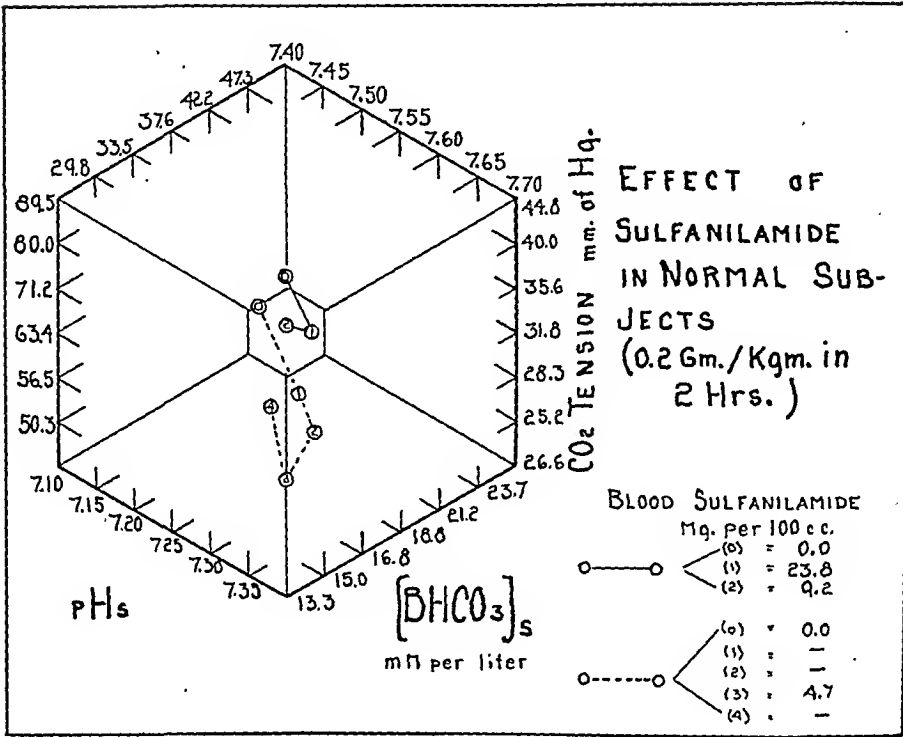


FIG. 10. Effects on the acid base balance in two normal subjects receiving a single dose of sulfanilamide equivalent to 0.2 gram per kilogram body weight.

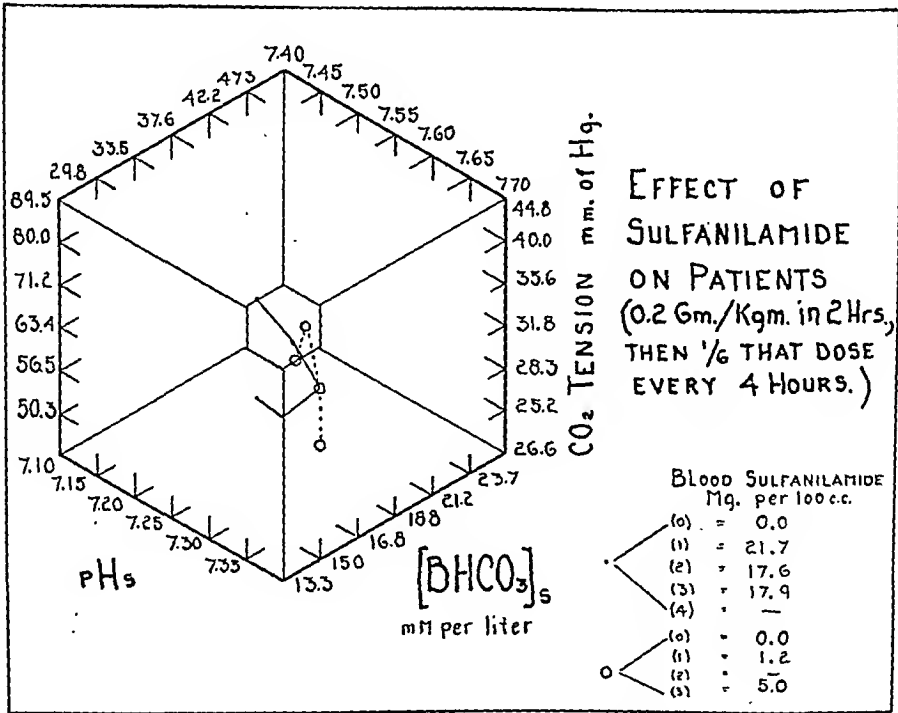


FIG. 11. Effects on the acid base balance of two patients receiving a single dose of sulfanilamide equivalent to 0.2 gram per kilogram body weight.

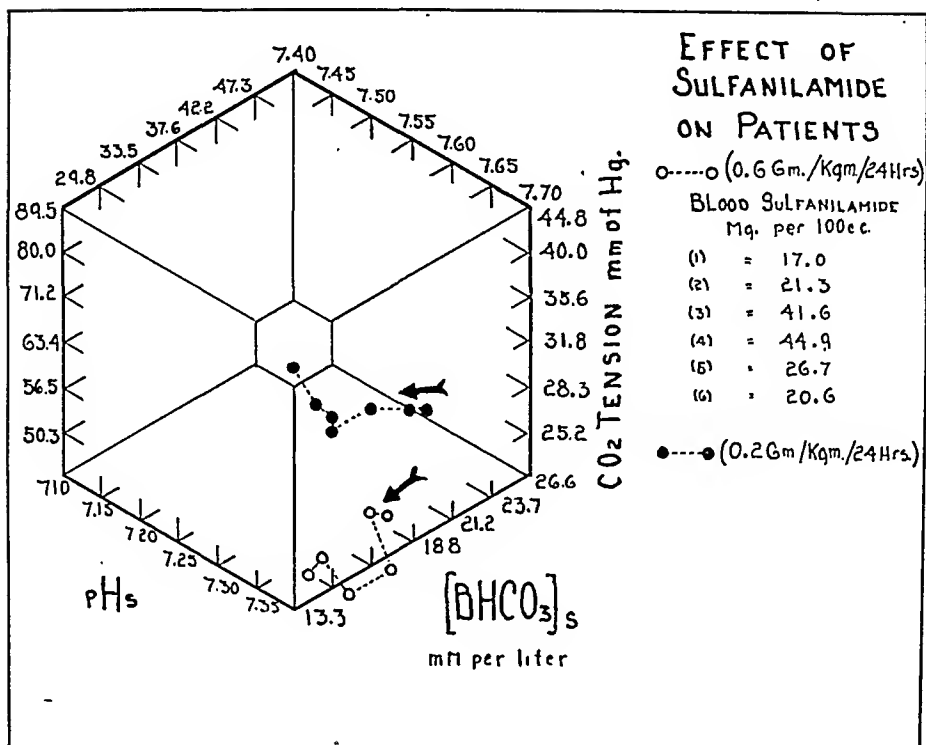


FIG. 12. Effects on the acid base balance of two patients receiving repeated doses of sulfanilamide. The gradual return of pH to normal in one instance occurred with continued reduction in BHCO_3 and in the other with similar return of BHCO_3 to normal.

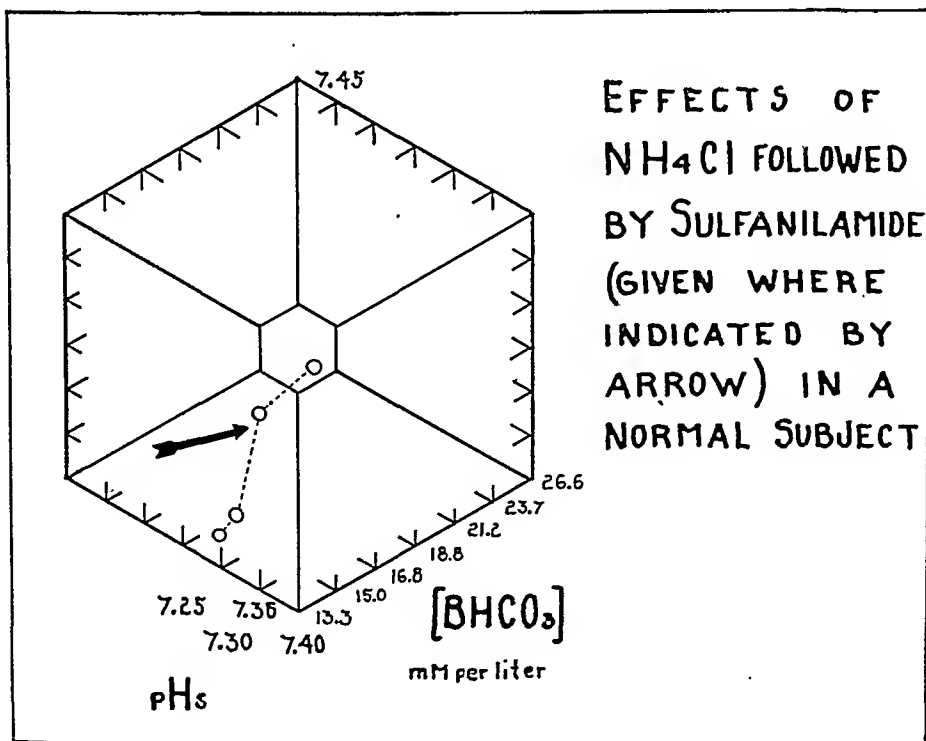


FIG. 13. Displacement of the acid base balance into the zone of acid excess (metabolic acidosis) by ammonium chloride administration. Later sulfanilamide administration deflected the pH toward normal, but, as should be expected, did not prevent the continued secretion of highly acid urine.

no logical use for alkali to be administered routinely with sulfanilamide "to prevent acidosis."

That the widespread use of alkali in sulfanilamide treated patients has not led to harm is to be explained both by the smallness of the amount of alkali which is usually administered and by the ability of the kidneys to excrete excess alkali. The dosage of sodium bicarbonate which has usually been recommended has been 10 grains with each dose of sulfanilamide, which would, therefore, average 60 grains, or four grams, daily. Normal kidneys *can* excrete excess alkali in concentrations equivalent to approximately 15 grams of sodium bicarbonate per liter of urine. One would, therefore, expect such doses of sodium bicarbonate merely to delay a little the compen-

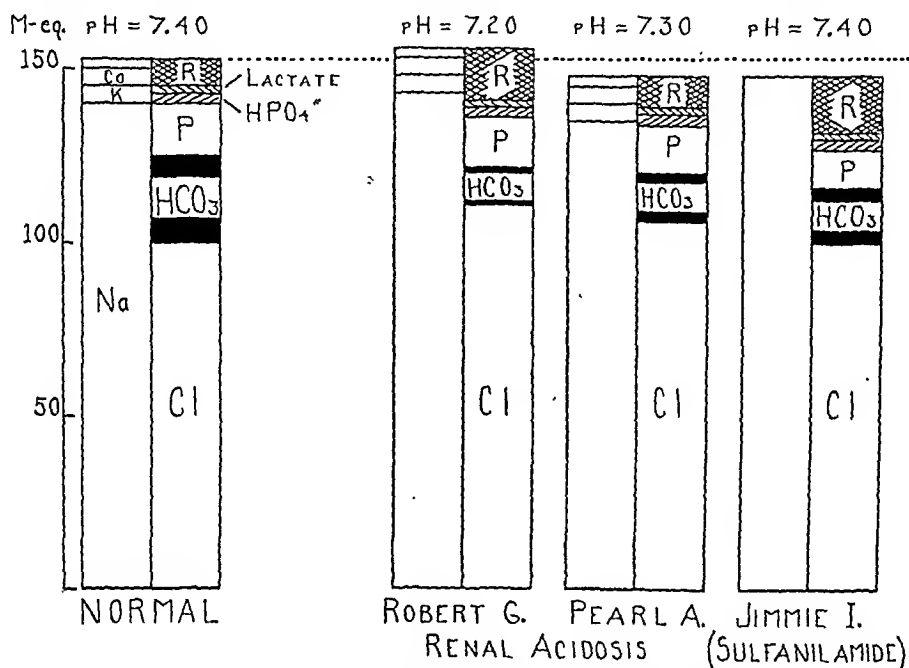


FIG. 14. Similarity of electrolyte patterns in states of BHCO_3 deficiency due to renal insufficiency (acidosis) and sulfanilamide administration (alkalosis).

sation for carbon dioxide deficit alkalosis. It should be mentioned, however, that such alkali administration might prove dangerous if conditions favorable for the development of the BHCO_3 excess type of alkalosis were present. Patients who became depleted of chloride, especially by prolonged vomiting, would tend to maintain normal total base concentrations by retaining BHCO_3 . Alkali administration with sulfanilamide would then tend to superimpose an increased degree of BHCO_3 excess alkalosis on a carbon dioxide deficit type. On the other hand, it should be recognized that the compensatory maintenance of an abnormally low plasma BHCO_3 level would hasten the development of a real acidosis, should conditions arise which primarily would lead to acidosis: i.e., renal failure, cardiac failure, ketosis, etc. Such situations will probably arise, if they have not already, inasmuch as the very conditions for which sulfanilamide is used, namely, severe in-

fections of various types, are such which not infrequently cause the development of severe acidosis. One, therefore, should be prepared to recognize a real acidosis if it develops and to treat it effectually. For its recognition determination of plasma pH may be necessary. In the absence of pH determinations, even completely determined electrolyte patterns of the blood plasma fail to distinguish between the effects of sulfanilamide and renal insufficiency (figure 14). It should also be mentioned that in the treatment of urinary tract infections with sulfanilamide, when due to *B. coli*, it seems advantageous from Helmholtz's observations¹⁰ to keep the urine alkaline. It should be noted from data previously presented^{3, 4} that when compensation for carbon dioxide deficit alkalosis produced by sulfanilamide administration is complete, urinary reaction shifts from alkaline to acid. If one at such a time wished to render the urine alkaline again, this could safely be accomplished by the administration of sodium *r*-lactate with Ringer's solution, which would make unlikely the possibility of a state of chloride deficiency and an alkali excess type of alkalosis. The use of the salts of Ringer's solution for the relief or prevention of this type of alkalosis has frequently been discussed.

SUMMARY AND CONCLUSIONS

Data concerning the effects of certain types of renal insufficiency and of sulfanilamide administration on the acid base balance have been presented which point to the following conclusions:

1. Plasma BHCO_3 reduction in chronic nephritis and other forms of renal insufficiency may occur with the production of a real acidosis of the "metabolic type" without abnormal acid retention, due fundamentally to inadequate reabsorption by the tubules of BHCO_3 from the glomerular filtrate.
2. Severe and persistent acidosis has been noted in an infant of four months in whom the only clearly demonstrable renal lesion seems to be failure of the tubules to reabsorb BHCO_3 .
3. There is a logical use for the administration of alkali, particularly as sodium *r*-lactate, in such cases, both to relieve and prevent recurrence of significant degrees of acidosis.
4. Plasma BHCO_3 reduction which follows sulfanilamide administration, on the other hand, must be looked upon as compensatory for a primary carbon dioxide deficit alkalosis.
5. There is no logical reason for the routine use of alkali with sulfanilamide to "prevent acidosis."

BIBLIOGRAPHY

1. SCHOENTHAL, L., and BURPEE, C.: Renal rickets, *Am. Jr. Dis. Child.*, 1930, xxxix, 517.
2. HASTINGS, A. B., and STEINHAUS, A. H.: A new chart for the interpretation of acid base changes and its application to exercise, *Am. Jr. Physiol.*, 1931, xcvi, 538.

3. BASMAN, J., and PERLEY, A. M.: Report of patients treated with sulfanilamide at the St. Louis Children's Hospital, *Jr. Pediat.*, 1937, xi, 212.
4. HARTMANN, A. F., PERLEY, A. M., and BARNETT, H. L.: A study of some of the physiological effects of sulfanilamide. I. Changes in the acid base balance, *Jr. Clin. Invest.*, 1938, xvii, 465.
5. SOUTHWORTH, H.: Acidosis associated with the administration of para amino benzene sulfonamide (prontylin), *Proc. Soc. Exper. Biol. and Med.*, 1937, xxxvi, 58.
6. LONG, P. H., and BLISS, E. A.: The use of para amino benzene sulphonamide (sulfanilamide) or its derivatives in the treatment of infections due to beta hemolytic streptococci, pneumococci and meningococci, *So. Med. Jr.*, 1937, xxx, 479.
LONG, P. H., BLISS, E. A., and FEINSTONE, W. H.: Mode of action, clinical use and toxic manifestations of sulfanilamide, *Jr. Am. Med. Assoc.*, 1939, cxii, 115.
7. BROWN, A. E., and BANNICK, E. G.: The use of sulfanilamide and prontosil solution, *Proc. Staff Meet. Mayo Clin.*, 1937, xii, 644.
8. MARSHALL, E. K., JR.: Determination of sulfanilamide in blood and urine, *Proc. Soc. Exper. Biol. and Med.*, 1937, xxxvi, 422.
9. COGGESHALL, H. C., and BAUER, W.: The treatment of gonorrheal and rheumatoid arthritis with sulfanilamide, *New England Jr. Med.*, 1939, ccxx, 85.
10. HELMHOLZ, H. F.: A comparison of mandelic acid and sulfanilamide as urinary antiseptics, *Jr. Am. Med. Assoc.*, 1937, cix, 1039.

THE NEUROCIRCULATORY CLINIC; A SUMMARY OF ITS ACTIVITIES

I. PERIPHERAL VASCULAR DISEASE*

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INTRODUCTION

No single form of therapy is equally applicable and efficacious in all forms of peripheral vascular disease. It is obvious that the physical therapist, the internist and the surgeon will strive to extend their sphere of activity in such a borderline field. This may not always be to the best interest of the patient. An approach to the solution of this difficulty seemed to be the establishment of a special clinic in which men from different departments group themselves around a problem which is neither medical nor surgical. It may have dermatologic, neurologic, ophthalmologic and orthopedic ramifications. The decision then as to whether a patient suffering from neurocirculatory disorder should be treated by physical therapy, by drugs, by surgical methods or by combination of these methods, rests on the joint opinion of men specially interested in this field.

While such a clinic was organized several years ago at Northwestern University and in 1935 at the University of Illinois, much inspiration has been derived from the Spleen Clinic at Columbia University¹ and the Thyroid Clinic at the University of Pennsylvania.² We believe that progress in the study of disease, improved facilities for undergraduate and postgraduate teaching and the opportunity for clinical research will be greatly furthered by the establishment of such group clinics throughout the country. It is the purpose of this communication to describe briefly our activities, the material studied, its classification, the guiding principles of treatment and the results obtained. In this first communication peripheral vascular disease will be discussed; other topics will follow in later reports.

MATERIAL STUDIED

We are reporting only the material seen during 1936 and 1937. A simple classification is shown in table 1.

Because of the character of our dispensary clinic there have been relatively few patients with acute arterial thrombosis and embolism. These were seen in private practice and furnished material for a separate report.³ Of the chronic arterial occlusions we have seen a comparatively large num-

* Received for publication December 20, 1938.

From the Department of Surgery, University of Illinois, College of Medicine, Research and Educational Hospital, and St. Luke's Hospital, Chicago. Aided by a Grant of the Council on Physical Therapy, American Medical Association.

ber of congenital anomalies; a previous report has been made of these ⁴ and the recent addition of eight cases to the original material has not changed our views or the therapeutic approach to them, except that a combination of ligations, injections and deep roentgen-ray therapy has been more frequently employed. The exclusion of the two above-named groups leaves the bulk of clinical material, as inflammatory arterial occlusions (Buerger's disease, syphilitic and rheumatic arteritis) and degenerative lesions (arteriosclerosis with and without diabetes). Arteriolar sclerosis with and without diabetes has been recognized with increasing frequency. Of the vasospastic group, a number of patients showing Raynaud's phenomena, but having detectable mechanical, endocrine or toxic etiology, such as cervical rib, paravertebral lymphadenitis, the scalenus syndrome, the hypothyroid and hypogenital vasospasms and the circulatory disturbances due to lead, arsenic or other intoxications have been excluded before the diagnosis of Raynaud's disease was made. Thus the three important and most frequent groups, whose management is the task of a vascular clinic, were Buerger's disease, obliterat-

TABLE I
Classification of Peripheral Vascular Disease

	<i>Organic</i>		<i>Functional</i>	
	Acute	Chronic	Vasospastic	Vasoparalytic
thrombosis		anomalies	neurogenic	erythromelalgia
		1. congenital		
embolism		occlusions	mechanical	
		1. traumatic	endocrine	
		2. inflammatory	toxic	
		3. degenerative		

ing arteriosclerosis and Raynaud's disease. We are limiting ourselves to a report on the value of various therapeutic procedures on this material. The observations reported here are based on 54 cases of Buerger's disease, 132 cases of obliterating arteriosclerosis, 36 cases of diabetic arteriosclerosis and 26 cases of Raynaud's disease.

All of these lesions, however, require subdivision according to the stage of the disease in which the patient is first seen and treated. Elsewhere one of us has shown ⁵ how important it is to determine the stage of Raynaud's disease when surgical therapy is contemplated. Such a classification, as suggested by Mr. Patterson Ross, ⁶ has been of great help to us in determining the operability of the patient and the results to be expected from sympathectomy in cases of Raynaud's disease. The first group consists of patients in whom there is no evidence of nutritional changes of the digits. The vessels are capable of a full and complete vasodilatation when subjected to heat, to vasodilators ⁷ or to a block of the vasoconstrictors by novocain. ⁸ The second group consists of patients who have some detectable structural damage; the digits are stiff and atrophic; there are stellate scars at the tips

of the fingers and there may be some sclerodactylia. Vasodilatation is still possible but it is incomplete and comes on slowly. To the third group belong patients whose finger tips are ulcerated, gangrenous or show a marked scleroderma. There is extensive arterial thrombosis in the vessels owing to the repeated and prolonged attacks of vasospasm and the capacity for vasodilatation is minimal or absent.

This classification deserves emphasis and wider recognition than it has hitherto obtained, as most clinicians and most textbooks teach that Raynaud's disease is a functional entity and that between attacks the circulation is perfectly intact. This may be true in the early stages; and even in the later stages the ulnar and radial arteries are patent. However, the digital arteries and their branches show organic damage and in evaluating the results of any treatment the stage of the disease and its natural course must be taken into consideration.

This classification can profitably be carried over to the occlusive group of arterial diseases, but several difficulties immediately present themselves. In the first place both Buerger's disease and obliterating arteriosclerosis obviously show organic damage and, with the exception of very early cases of Buerger's disease, are incapable of full vasodilatation. Secondly, it is usually only the lower extremities which are affected by occlusive disease. Different clinical groups must be established which can be easily detected and readily separated from each other. While it is still important to determine whether or not in a given patient suffering from occlusive arterial disease, the capacity of the vascular bed to dilate is still maintained or gradually diminishing, the bulk of peripheral vascular patients, namely those suffering from advanced stages of Buerger's disease, from diabetic endarteritis or arteriosclerosis, are more usefully classified from a different point of view. The spastic element here is not impressive. For this reason the following classification has been adopted for patients suffering from organic arterial disease.

Group 1: Patients who have an oscillometric index of over one-half cm. at the ankle, who complain of claudication after walking five blocks or more and who have no pain at rest.

Group 2: Patients with an oscillometric index under one-half, who complain of claudication within two blocks and who have no pain at rest.

Group 3: Patients who have continuous pain at rest, show no or minimal oscillations at the ankle, and have signs and symptoms of ischemic neuritis.

Group 4: Patients who have actual gangrene with no oscillations at the ankle.

Obviously there are borderline cases as there may be some variation of these criteria from day to day. Attention must also be called to Group 4, in which a gangrenous digit with good oscillations at the ankle deserves an entirely different consideration and has a different prognosis. Such is the

case in diabetic endarteritis with a digital gangrene which can be readily incised, drained and healed in contrast with the case with popliteal atheroma causing digital gangrene in which a major amputation is necessary.

The real value of this classification can be illustrated during the discussion of therapeutic results since the different groups respond in proportion to the degree of structural involvement.

THE PRINCIPLES OF TREATMENT

GENERAL CARE

Every patient is examined by a member of the Department of Medicine. Wassermann and Kahn tests are carried out in every case. Blood counts and sedimentation rates are observed to gauge the activity in Buerger's disease and phlebitis. In a large series of determinations, however, carried out under the direction of Dr. S. O. Levinson, such marked fluctuations were encountered that a routine use of sedimentation rates did not seem advisable. Diabetes is controlled by the metabolic clinic; fasting blood sugars are taken on all arteriosclerotics to rule out a mild senile diabetes with high kidney threshold for sugar. The condition of the heart and kidneys has been studied by Drs. Ford K. Hick and Harold A. Lueth of the Department of Medicine. Endocrine factors are discussed with the men interested in endocrinology. Static disturbances of the feet are sent to the Orthopedic Department for consultation. In women exhibiting Raynaud's phenomena, a roentgen-ray for cervical rib and a basal metabolism test are obligatory. Urine and blood are sent to the Department of Chemistry for lead and arsenic tests. Neurologic and psychiatric consultations have been frequently sought; they proved especially valuable in patients exhibiting Raynaud's phenomena and in atypical neuralgias lacking somatic distribution. A high vitamin, well balanced diet is prescribed all patients unless special requirements must be met. They are urged to drink 12 glasses of water unless contraindicated by cardiac or renal impairment or local edema formation. The use of tobacco is absolutely forbidden in Buerger's disease and moderation in its use is advised in arteriosclerotics. To break up the tobacco habit lobelin has been tried but with little success. Denicotinized cigarettes are a help in breaking the nicotin habit.

LOCAL CARE OF THE FEET

A printed sheet, which is the one used in the vascular clinic of the Cincinnati General Hospital, is given to each patient (table 2).

PHYSICAL THERAPY

Heat is used continuously in the form of a simple electric baker, which can be readily improvised at home or in the hospital. If the patient is ambulatory, the baker is used throughout the night. Most patients suffering

from arterial occlusions are comfortable in a temperature between 85° and 90° F., but occasionally the optimal temperature is lower than that. Alternate hot and cold baths are not used. They tire the patient, macerate his skin, should not be used in the presence of gangrene, and may even aggravate vasoconstriction. A warm soak for 15 to 20 minutes, preferably with a mild antiseptic such as a 1:8000 solution of potassium permanganate, is useful before going to bed and controls the often co-existing ringworm infection. The ringworm infection is frequently the starting point of serious infection, gangrene or loss of digits and limb.

TABLE II

General Directions for Home Care of the Feet

The directions are naturally modified according to individual requirements. The outline is that of the Vascular Clinic of the Cincinnati General Hospital.

1. Wash feet each night with neutral (face) soap and warm water.
2. Dry feet with a clean soft rag *without* rubbing the skin.
3. Apply rubbing alcohol (70 per cent) and allow the feet to dry thoroughly. Then apply a liberal amount of vaseline or toilet lanolin and gently massage the skin of the feet.
4. *Always* keep your feet *warm*. Use woolen socks or wool-lined shoes in the winter and white cotton socks in warm weather. Use a clean pair of socks each day.
5. Use loose-fitting bed socks instead of hot water bottles, electric heaters or any other form of mechanical heating devices.
6. Wear properly fitting shoes and be particularly careful that they are not too tight. Use shoes made of soft leather and without box-toes.
7. Cut your toe nails only in very good light and only after your feet have been cleansed thoroughly. Cut the toe nails straight across.
8. Do not cut your corns or callouses.
9. Do not wear circular garters.
10. Do not sit with your legs crossed.
11. Do not use strong antiseptic drugs on your feet. Particularly *never* use tincture of iodine, lysol, cresol or carbolic acid.
12. Go to your doctor at the first signs of a blister, infection of the toes, in-growing toenail or trouble with bunions, corns or callouses.
13. Drink at least four quarts of water each day.
14. Eat plenty of green vegetables and fruit in an otherwise well-balanced, liberal diet, *unless* you have been ordered to follow some special diet.
15. Do not use tobacco in any form.
16. Have some member of your family examine your feet at least once each week.
17. Carry out the exercises prescribed by your doctor exactly as you were taught to do them in the Clinic. Do them regularly and faithfully.

Postural exercises have a sound foundation, and an oscillometric curve can readily demonstrate the effect of posture on pulse-volume (figure 1). The patient may take active postural exercise or elevate his leg with the help of a pulley, which saves a lot of oxygen that would otherwise go to nourish the contracting muscle. An automatically oscillating bed has also been used in both of our clinics * but seems too expensive for general use.

Massage is a time-honored method to improve circulation. In the absence of venous or recent arterial thrombosis, and when the skin is intact, mild massage may produce a reactive hyperemia. As will be discussed below, we have far more efficient methods to produce reactive hyperemia. In our clinic, chiefly for economic reasons, we have made little use of massage.

* Some of the material has been seen at St. Luke's Hospital.

B. Result of position on pulsation

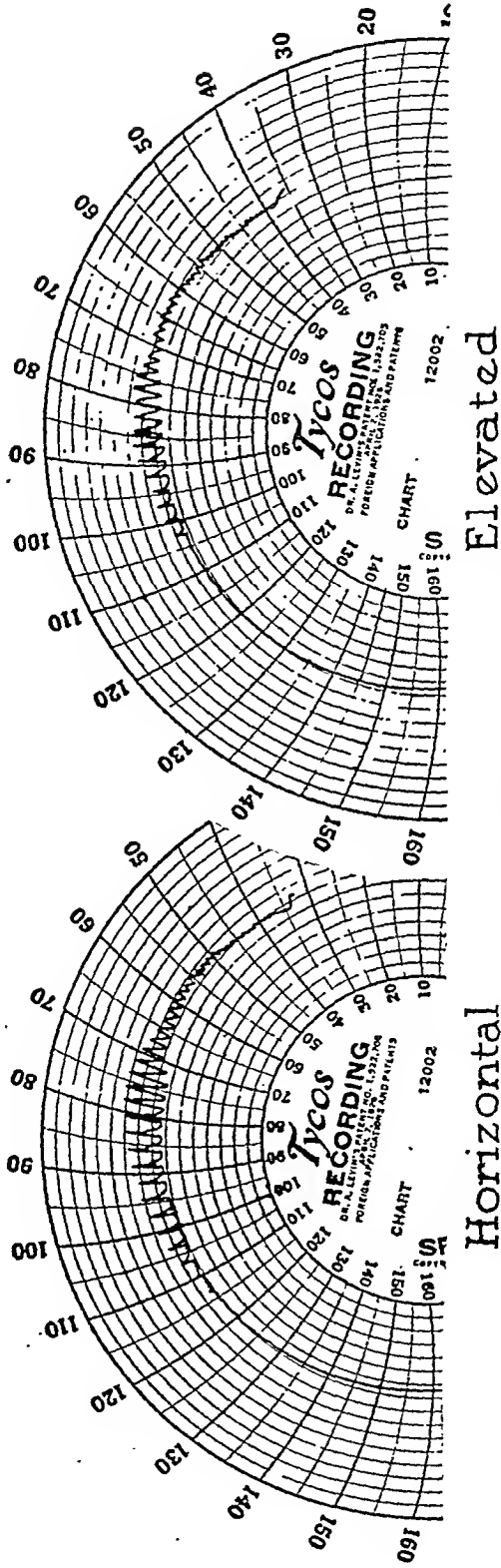


Fig. 1. The effect of posture on the oscillometric curve. Oscillometric curves taken at the ankle of August M., 29 year old male, with normal peripheral circulation.

Diathermy treatments have been given since 1931 to a large number of patients. Coulter, Osborne and one of us have studied the temperature reactions of a large group of normal controls and of a series of patients suffering from various types of peripheral vascular disease. To heat up the lower extremity, electrodes are placed on the abdomen and the lower part of the back. For the treatment of the upper extremity, the electrodes are placed on the side of the neck and the upper dorsal spine. Thus not only is the blood being heated as it passes through the root of the limb, but a reflex vasodilatation is produced (figure 2). We would warn against the use of

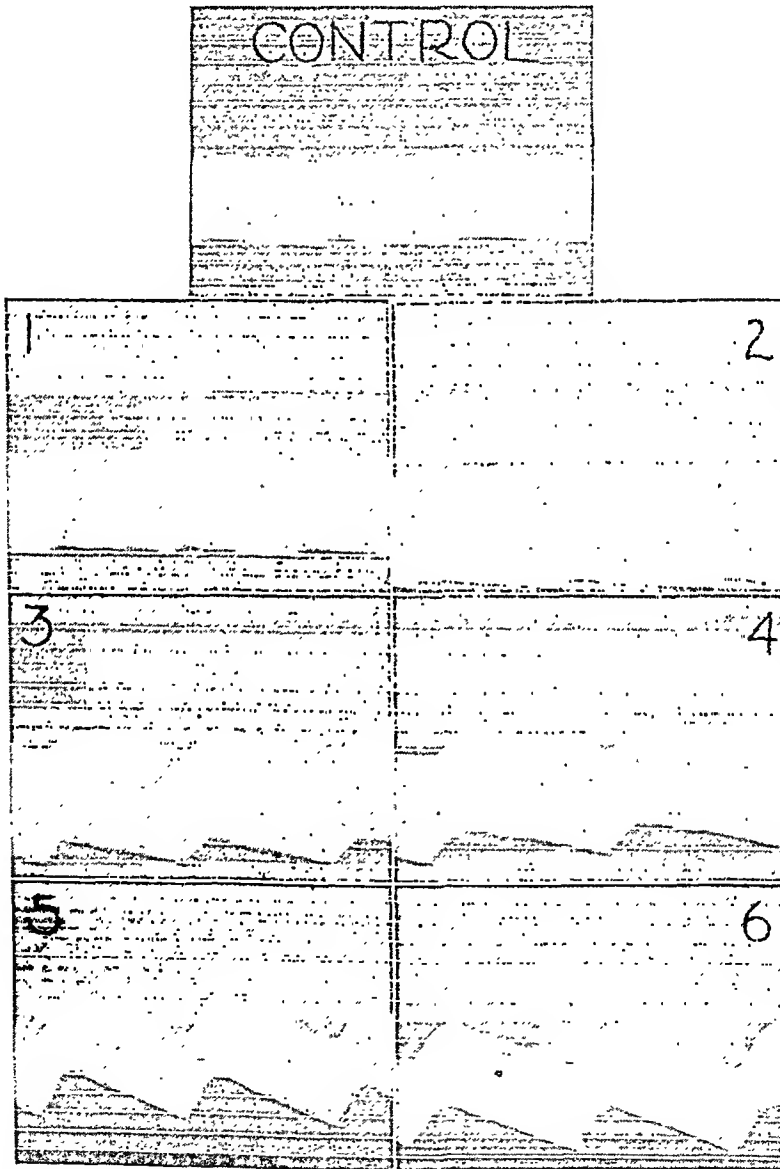


FIG. 2. Plethysmographic curves of right big toe during lumbar diathermy, 1000 M.A. for one and half hours. Top curve: control reading after 30 minutes of rest. A reading was made every 15 minutes, using Johnson's plethysmograph. Note that the real increase in pulse volume occurred only after one hour of treatment. Patient A. T., 39 years old, suffering from Buerger's disease with marked vascular spasm. From unpublished data of Coulter, Osborne and de Takats, 1931.

electrodes on the affected limbs as they are predisposed to burns. More recently, however, the use of large heat cradles has supplanted the diathermy treatments, as they are almost as effective and much cheaper. These reflex heat treatments are advantageously combined with the newer mechanical ways of stretching the vessels, such as suction and pressure or intermittent venous occlusion.

Short wave therapy should be even more effective than conventional diathermy. Again, applying it to the root of the limb, both a direct heating effect and a vasomotor influence are obtained. It is unwise to use it on the affected extremity.

Iontophoresis of vasodilators such as histamine, acetylcholine and mecholyl has been used in our clinic for a period of years. Finally only mecholyl has been retained and is used chiefly in scleroderma and in thrombophlebitic indurations. Table 3 summarizes our results with mecholyl iontophoresis

TABLE III
The Effect of Mecholyl-Iontophoresis in Scleroderma

Patient	Stage of Disease	Number of Treatments	Result
Dale L.	3	15	Died of nephrosclerosis
Catherine K.	2	50	Marked improvement compared with control side, which was sympathectomized
Ester S.	2	50	Marked improvement
Elizabeth S.	1	78	Marked improvement
			Both arms treated
Margaret W.	1	15	Definite improvement on treated side

Stages of disease: 1 = early involvement of symmetrical areas on face, chest wall, arms or hands. 2 = ulceration on finger tips, over elbows, calcareous deposits. 3 = visceral involvement, low blood sugar and nitrogenous retention. Endocrine glands, kidney and pleura are often involved.

in scleroderma.* It should be mentioned that no other treatment directed against scleroderma has proved to be so efficient in softening the indurated skin. Equally helpful were the percutaneous applications of mecholyl in thrombophlebitic indurations,† but only at the stage when the acute inflammatory stage had subsided; in the more acute hyperemic indurations, with increased skin temperature and a great deal of tenderness, small doses of roentgen-ray were far more effective.

DRUG THERAPY

A number of vasodilators have been used; mecholyl has already been discussed. In patients suffering from acute arterial occlusion rapidly acting drugs, such as the nitrites⁷ and papaverine⁹ have been given intravenously;

* Sclerodactylia, secondary to chronic ischemia, has not been included. True scleroderma has been found very infrequently in this group.

† The use of normal salt solution applied to the negative pole is even more effective than mecholyl (de Takats and Strunk, unpublished data).

the former in one grain, the latter in one-half grain doses, not more than three times a day for three or four days. The insulin-free pancreatic extract (Padutin and Kallikrein of the German authors) has been tried in a small series of cases, but with so little objective or subjective benefit that its administration was discontinued. Tissue extracts have been too costly for use in the free clinics. In private cases there seemed to be a slight temporary improvement in claudication, but the injections are painful and not any more effective than nonspecific parenteral protein therapy. In all chronic organic vascular occlusions, theobromine or one of its salts (gr. 30 daily) combined for mild sedation with one-quarter of a grain of phenobarbital has been administered. In the arteriosclerotic group this medication was felt to be as appropriate for the coronary and renal vascular sclerosis as for that in the peripheral vessels. The occasional patient who could not take theobromine by mouth because of gastric distress was given keratin coated theobromine or aminophyllin. In patients with severe pain, morphine has been strenuously avoided except before amputations. Amidopyrin gr. 5, with codein gr. one-half three times a day seemed sufficiently effective until some more direct attack was made on the intractable pain. These measures will be discussed under surgical treatment.

Intravenous injections of *triple typhoid vaccine* have been used. In a previous article one of us¹⁰ pointed out that to obtain peripheral vasodilatation, the massive doses producing chills and fever are unnecessary. Starting with one million bacteria and slowly increasing the dose in biweekly injections until a course of 12 injections had been given seemed beneficial in the acute inflammatory stages of Buerger's disease and in migrating phlebitis. Occasionally, however, a patient seems entirely refractory to this type of treatment. The small dose is enough to produce vasodilatation, perhaps a delayed rise in temperature on the second night after the injection, and a moderate leukocytosis. It might act as a nonspecific desensitizer to an unknown but specific agent.

Sodium chloride has been given in doses of 10 grams (150 grains) to patients showing an inspissation of blood or decreased blood volume as encountered in Buerger's disease. In this respect a small series of cases studied by the Congo-red method in 1931 is presented in the adjoining table (table 4). Whereas the intravenous use of 5 per cent sodium chloride does temporarily increase blood volume and also the size of oscillations, the effect lasts hardly over one hour. When the patient consumes large amounts of water and retains it better with the addition of sodium chloride, a similar effect can be obtained and the disadvantages of frequent intravenous infusions may be avoided. Diets low in potassium enhance the value of the high sodium diet.¹¹

Alcohol. The sedative and vasodilator action of moderate doses of alcohol is well known. Actually it is easy to demonstrate the rise in skin temperature and the increased oscillations following the intake of an alcoholic beverage (figure 3). For those who are used to taking a highball or cock-

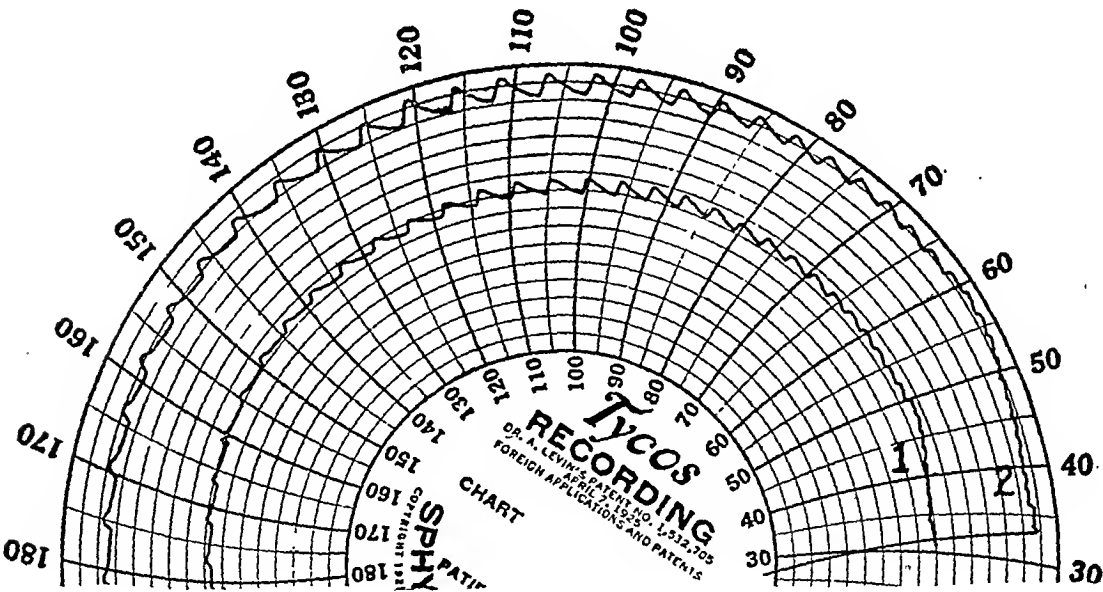
TABLE IV

Blood Volume in Buerger's Disease
Note that red counts are high, total blood volume and plasma volume are low, hematocrit values are high indicating loss of plasma.

Case	Weight in Kilograms	Red Blood Cells	Hemoglobin	Total Blood Volume	Plasma Volume	Cells by Hematocrit Per Cent
1	67	5,300,000	85%	5100 (76.1)*	2840 (42.4)*	45
2	62	4,900,000	85%	4900 (79)	2200 (35.4)	44
3	77	5,100,000	94%	6333 (82.2)	3800 (49)	41
4	61	5,600,000	95%	5200 (85.2)	2300 (37.5)	59
5	60	5,200,000	94%	5100 (85)	2600 (43)	50

* Figures in parentheses indicate volume in cubic centimeters per kilogram.

C. Effect of alcohol



- 1. Normal
- 2. Following ingestion 1 oz. alcohol

FIG. 3. Oscillometric curve taken at the ankle in F. St., 50-year-old male, suffering from Buerger's disease with demonstrable vascular capacity to dilate. The second curve indicating increased pulsation was obtained 1/2 hour after the ingestion of an ounce of whiskey.

tail before dinner, temporary increase in circulation can be agreeably obtained. Whether it has a slowly accumulating beneficial effect on the reserve capacity of the vascular bed is doubtful. That occasional drinkers who were told that alcohol will help their circulation have become habitual drunkards has been repeatedly observed.

Iodides have been used empirically in arteriosclerosis for a long time. The effect of an iodide on gummatous lesions is well known. Evidence that it reduces blood viscosity or that it links itself with blood lipoids and therefore inhibits lipid deposits in the early stages of human atheromatosis is not conclusive. It has been shown, however, that both iodine and thyroid extract prevent experimental atherosclerosis produced by feeding of cholesterol to rabbits.¹² Clinically, the intermittent administration of iodides to arteriosclerotics may be of benefit; we have, however, no controlled observations in regard to their value. Prolonged, continuous administration may even do harm by suppressing thyroid activity.¹³

Mercury. A 33 per cent mercurial ointment (blue ointment U. S. P.) has been used in the migrating phlebitis of Buerger's disease. Just as in the tubular forms of lymphangitis, the salve has a definite effect on the absorption of the perivenous edema. Mercurial dermatitis must be watched for and the salve immediately discontinued. Just like iodides, the mercurial salve is a time-honored remedy; whereas its mechanism of action in inflammatory exudates is not clear, its clinical value is impressive.

PASSIVE VASCULAR EXERCISES

Since 1934, four apparatuses have been used in the two clinics, one producing a Hermann type of negative and positive cycle, and three producing the Landis type of curve. In a previous communication¹⁴ we have tabulated a few data regarding the oxygen-saturation of the femoral vein before treatment, after 20 minutes and after 40 minutes of therapy. From these data it was apparent that apparatus B, the pavex machine, was the only one in which venous stasis could be avoided; during the use of the other three apparatuses, however, a continuous mild venous stasis was present which could be duplicated by a compression with 40 mm. of mercury for 40 minutes. More important, however, than the type of apparatus used was the stage of the disease at which suction and pressure treatments were started. Veal and McCord¹⁵ pointed out that if after an hour of treatment an increase in oxygen saturation does not occur, the prognosis is poor and the treatments will not be effective. This would be a most logical method of selecting cases for treatment, but it has not been found applicable as yet to a large group of clinic patients. Instead, we made a statistical inquiry into the early and late subjective and objective results of treatment in the four groups of obliterative vascular disease. Skin temperatures and oscillometric readings were taken before and after the completion of an individual treatment and a series of treatments. Treatments were given for one hour two

or three times a week, this being the maximal capacity of our present space and personnel. It was soon found that in the absence of a room with controlled temperature and humidity the temperature readings meant very little. While it is true that following the use of either suction apparatuses or after intermittent venous occlusion the skin temperatures rose, the same trend of rise was demonstrable if the patients simply were placed on the bed for one hour and their legs placed in the boot for another hour without suction and pressure. At the end of the two hour period their skin temperatures were not any lower than after suction and pressure treatment (figure 4). The value of temperature measurements, then, to indicate improvement of circulation following suction and pressure treatment is doubtful. We have abandoned the measurement of skin temperatures in connection with suction and pressure therapy and tried to evaluate the results according to the subjective improvement and the capacity for vasodilation. The opinion of the patients often conflicts with the objective measurements and we have finally come to grade the improvement on the basis of (1) return of pulsation, (2) increased oscillometric readings, (3) increased claudication time, and (4) the healing of ulcers or small areas of gangrene. While a detailed study of these results will be published elsewhere, we are here presenting a summary of our findings (table 5) which permits the following conclusions. In the

TABLE V

Results Obtained with Suction and Pressure Therapy in the Treatment of Obliterative Vascular Disease

Notice that the degree of improvement depends on the stage of the disease in which treatment is started

Stage of Disease	Number of Patients	Improvement						Discontinued After 10 Treatments
		After 10 Treatments			After 50 Treatments			
		Marked	Slight	None	Marked	Slight	None	
1	4	3	1	—	3	1	—	0
2	42	12	28	2	6	14	6	16
3	41	4	10	27	6	6	8	21
4	13	—	—	13	—	—	—	13
	100	19	39	42	15	21	14	50

Stages of obliterative peripheral vascular disease: 1 = oscillometric index $< \frac{1}{2}$, claudication 5 blocks; 2 = oscillometric index $\frac{1}{2}$, claudication 2 blocks; 3 = oscillometric index 0, rest pain; 4 = oscillometric index 0, gangrene.

first group of patients both the early and late results were good. Unfortunately, patients who can still walk five blocks without claudication seldom seek medical advice, especially in dispensary clinics. In the second group the response after 10 treatments was definite; only 4.8 per cent showed no results, but results are less impressive after 50 treatments. In the later

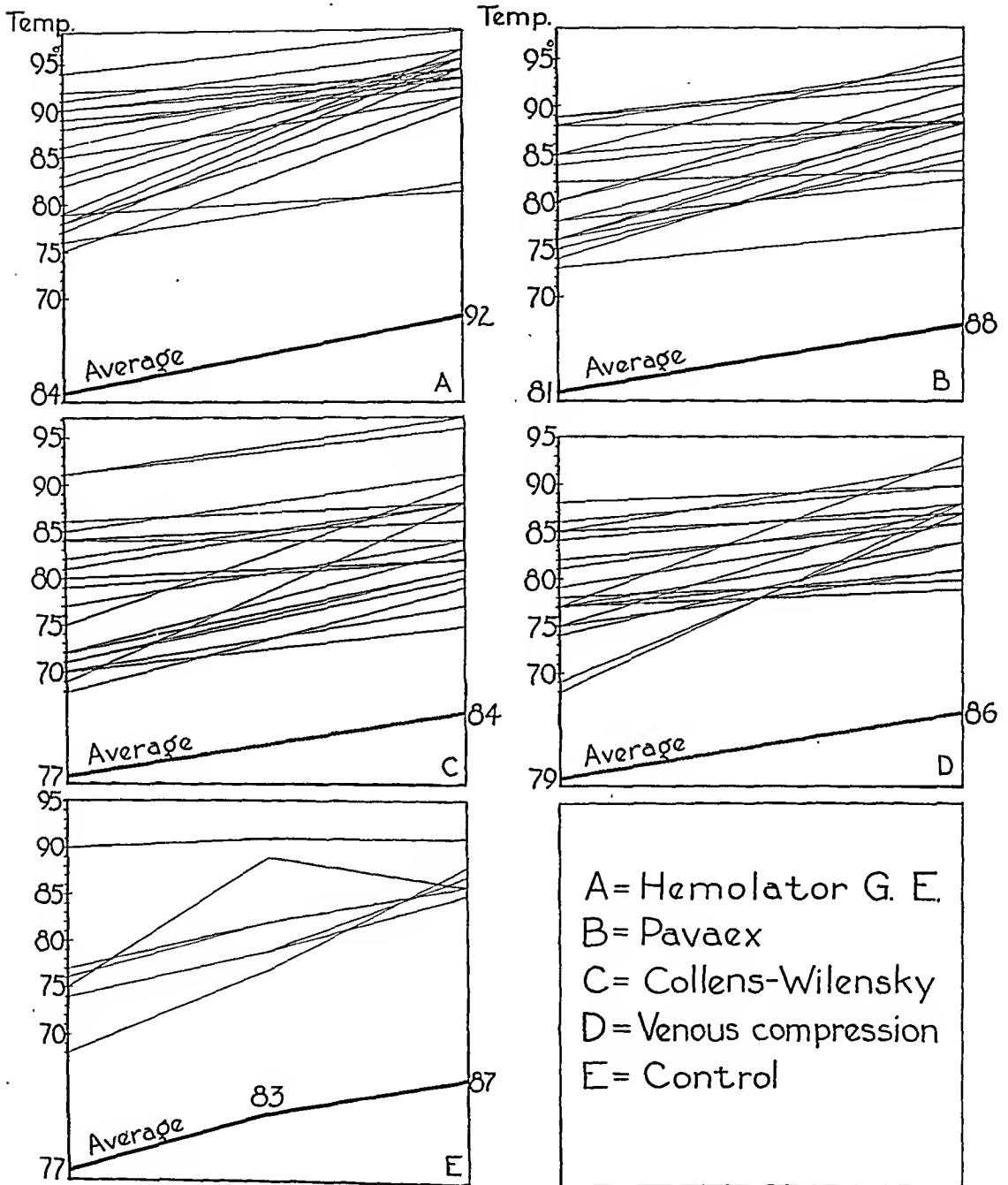


FIG. 4. Readings of skin temperature before and after various forms of vascular exercise given for one hour. The readings were made with a General Electric electric thermometer. Twenty patients were studied in each series but only a few of the controls are shown. In the control series, the first reading was taken on entrance, the second after one hour of rest, the third after one hour in a boot, without the suction and pressure. Obviously the rise in temperature continues on resting for much longer than one-half hour, which is the customary period of rest before measurements of skin temperature are taken. Previous reports on the rise of skin temperature after treatment with one of these devices must be interpreted with caution.

stages, larger and larger percentages of failure are encountered. Perhaps the most enlightening are the figures on patients who discontinued their visits after 10 treatments. They are exactly one-half of the patients who started out with 10 treatments. Whereas in the first group none stayed away, in the second group 38 per cent discontinued their treatments, in the third group 50 per cent did not come back, and the fourth group could not be followed at all after the first 10 treatments; they either died or were subjected to amputation of the affected limb. In all fairness to the method it must be stated that some patients stayed away because of reëmployment, some found it too hard to come for treatments two to three times a week, and some looked for other medical advice. But as a general trend it can be stated that roughly one-third of the second group, one-half of the third group and all of the fourth group voluntarily discontinued treatment.

In order to save unnecessary effort on the part of the patients we now refer them for suction treatment if they belong to groups one and two. If they belong to group three, 10 treatments are given as a therapeutic test and those who show marked or slight improvement after 10 treatments are given at least 50 treatments, but preferably a hundred. As stated in a preliminary report¹⁶ patients with Buerger's disease were not favorably affected by suction and pressure therapy. We must qualify this statement now and say that following sympathectomy, the steady use of suction and pressure therapy is capable of bringing about improvement according to the stage of disease in which they are found to be.

It seemed obvious that if one could substitute suction and pressure therapy with some simple, inexpensive method, which could be used daily at home for a long period of time, a real service would be rendered especially to the indigent ambulatory population of the dispensaries. For this reason we equipped both clinics with a simple eight-inch cuff with the help of which intermittent venous hyperemia could be produced as described below.

INTERMITTENT VENOUS HYPEREMIA

In a previous communication¹⁴ this method of alternating constriction and release, which was first described by Thies¹⁷ in 1913 as a modification of Bier's hyperemia, was analyzed. We have since equipped 50 individuals or county nurses with this device, the purpose of which is to enable large groups of people often living in small communities or on farms to use daily vascular exercise for long periods of time. It was difficult to obtain follow-ups on this group of patients as so many of them lived at great distances and could be followed only by mail. However, we obtained through personal re-examination or through the help of a questionnaire results on 35 patients which are tabulated (table 6). These figures are, of course, not comparable with the ones given showing the results of suction and pressure therapy. Even with careful grading no two cases are alike; furthermore, we have only few data on the benefits obtained after 10 treatments, so that they could not

be included. Then again, patients in group 4 were not subjected to this treatment as it was felt, because of our previous experience with suction and pressure therapy, that they could not be helped. In addition to all this, the number of cases is too small to permit a comparison. Nevertheless, a certain similarity of the two tables is unmistakable. Groups 1 and 2 did better, group 3 not so well. There are some advantages and disadvantages of this method as compared with the suction and pressure therapy. It is inexpensive, and can be carried on for months far away from hospital centers; one leg can be treated in the morning and the other one in the evening. Although we have seen patients who have conscientiously carried on for four to six months, piling up 150 to 200 hours of treatments and getting surprising benefit, most patients do find it cumbersome and especially if some improvement is noted will readily discontinue treatment. This is its disadvantage compared with mechanized forms of treatments. Then also the acute occlusions and the threatening gangrenes require four to five hours of

TABLE VI

Results Obtained with Intermittent Venous Hyperemia in the Treatment of
Obliterative Vascular Disease

Note again the poor results obtained in later stages of obliterative vascular disease.

Stage of Disease	Number of Patients	Results of 50 Treatments			Discontinued
		Marked	Slight	None	
1	5	4	1	—	0
2	16	5	8	1	2
3	14	5	6	2	1
4	0	—	—	—	—
	35	14	15	3	3

continuous treatments, and in such cases the suction and pressure therapy is certainly superior. We would formulate at present our choice between these two methods as follows: (1) hospitalized patients, especially those requiring several hours of treatment, are given suction and pressure therapy, (2) ambulatory patients, especially those living far from hospitals or who cannot afford a long series of treatments, are given the inflatable cuff. The same is given to patients who have undergone sympathectomy for Buerger's disease or who have had one leg amputated and the other showing the first or second stage of vascular occlusion.*

In a recent article Allen and McKechnie¹⁸ stated that they were unable to find a consistent rise in skin temperature following intermittent venous occlusion and hence they do not believe that a significant vasodilation fol-

* Since this article went to press, considerable use has been made of an automatic device, which allows inflation and deflation of cuffs on both extremities and may be used for several hours daily.

lows its use. This we believe does not prove or disprove an increase in vascular capacity, a stretching of the venocapillary bed, which has been the aim of such treatment. Increased blood flow and increased vascular capacity are by no means synonymous. Increased blood flow could hardly be expected after one treatment, but gradual stretching of the vascular bed is obvious from oscillometric readings.¹⁴

SURGICAL TREATMENT

Sympathectomy. Indications for sympathetic ganglionectomy have gradually crystallized in our clinics and are summarized in table 7. The analysis

TABLE VII

Indications of Sympathectomy for Peripheral Vascular Disease
1928-1936

These indications have gradually crystallized after studying the results of surgical and conservative treatment

Diagnosis	Selection of Cases
Raynaud's phenomena	Lack of marked structural changes Absence of sclerodactylia Stages 1 and 2
Buerger's disease	Absence of acute inflammatory stage Below 40 years of age with definite collateral reserve Poor response to conservative treatment
Poliomyelitis	Moderate paralysis limited to one extremity; evidence of vasospastic phenomena Age preferably between 6 and 10 years
Reflex dystrophy (causalgia, traumatic vessel spasm, Sudeck's atrophy)	Severe cases producing disability, resistant to physiotherapy, exhibiting abnormal vasomotor phenomena
Unclassified	Rapid onset of digital thrombosis with impending gangrene Mostly upper extremities involved

of results has been published in other articles.^{19, 20} For the sake of avoiding repetition we wish to present three graphs which illustrate the percentage of failures following sympathectomy as affected by the diagnosis, the stage of the disease and the type of operation (figures 5, 6, 7). There is an unmistakable improvement in our figures as case selection and technic improve, and after-treatment is carefully followed out. Generally speaking, the effect of sympathectomy on the circulation of an extremity simply consists of stabilizing blood flow by freeing the limb from any vasomotor activities which serve the purpose of heat regulation. Thus blood can really be utilized for nutritional purposes and for nothing else. Arguments in favor of this statement may be found in the above quoted articles. A summary of results which have been obtained is shown in the next table (table 8).

Paravertebral Nerve Block. One of us (W. C. Beck) has studied the effect of paravertebral alcohol injections which were given in the region of the lumbar sympathetic chain from the first to the fourth lumbar segment.

Failures of sympathectomy
affected by preoperative diagnosis

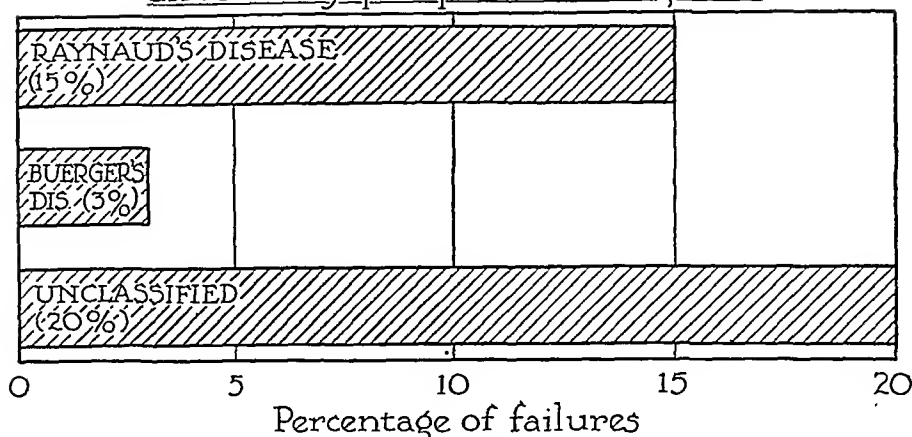


FIG. 5. Percentage of failures following sympathectomy as affected by preoperative diagnosis. Failure of sympathectomy for Raynaud's disease has been registered when there was no amelioration of symptoms but a standstill or progress of the disease. When patients suffering from Buerger's disease were subjected to sympathectomy, the operation was called a failure if ulcers remained unhealed, gangrene progressed or amputation became necessary. Sympathectomy seldom improves intermittent claudication. In the unclassified group we spoke of failure when impending gangrene has not been arrested or no amelioration of symptoms has occurred. Note that the greatest percentage of failures occurred in the unclassified group, which indicates that in some of these cases sympathectomy was not clearly indicated. The 15 per cent failure in Raynaud's disease is largely caused by some of the earlier operations on the cervicothoracic chain, which are not done any more. The small percentage of failures in Buerger's disease is probably due to our restricted indications (see table 7).

Failures of sympathectomy influenced by degree
of structural involvement — 105 operations 1928-1936

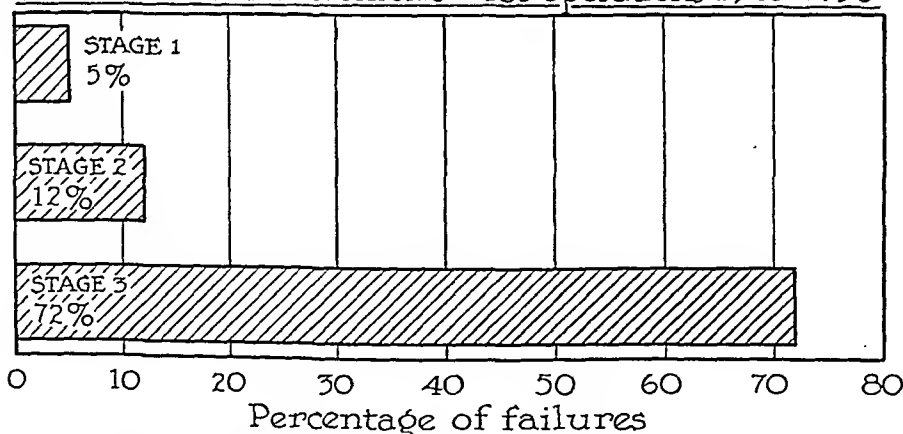


FIG. 6. Percentage of failures following sympathectomy as affected by the stage of the disease. Stage 3, indicating purely organic involvement with minimal capacity of the vessels to dilate, is obviously a poor indication for sympathectomy. It was employed only in a few such cases as a desperate attempt to prevent amputation. This chart emphasizes that the outcome of sympathectomy depends mainly on the degree of structural involvement. Failure to prevent amputation is frequent in the advanced stages of organic vascular disease.

This method was used in patients suffering from Buerger's disease, who were past the age of 40, showed little collateral reserve and were not thought

Failures following different types of sympathectomy
105 cases 1928-1936

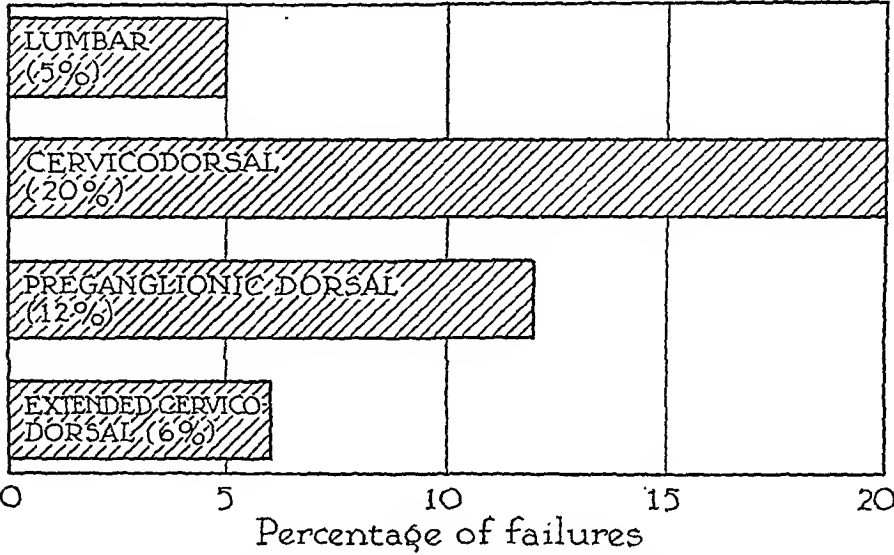


FIG. 7. Percentage of failures following sympathectomy as affected by the type of operation. The classic cervicodorsal and the pre-ganglionic dorsal sympathectomies have been followed by a noteworthy percentage of recurrence so that at present only the typical lumbar and an extended cervicodorsal sympathectomy are performed. This graph illustrates the importance of technically complete operations.

TABLE VIII
Results of Sympathectomy for Peripheral Circulatory Disturbances *
1928-1936

Diagnosis	Number of Patients	Number of Operations	Success	Im-provement	Failure	Mor-tality
Raynaud's disease	10	26	17	4	5	
Buerger's disease	21	56	49	4	2	1
Poliomyelitis with vessel spasm	3	3	3			
Reflex dystrophy (causalgia, osteoporosis)	10	10	10			
Unclassified	6	10	7	1	2	
Total	50	105	86	9	9	1

* Only one patient was lost, a patient with Buerger's disease operated on in 1929, who died of a coronary thrombosis five days after the operation. According to our present criteria, he should not have been subjected to sympathectomy because of his age (50) and the amount of structural damage, especially in the visceral organs. Success indicates symptoms relieved and ability to return to full work; improvement indicates pain relieved, circulation improved but full working capacity not restored; and failure indicates no appreciable improvement after operation or amputation.

suitable for sympathectomy. It was also used as advocated by Reichert²¹ to control the pain of arteriosclerosis obliterans. Evidence of sympathetic block such as drying of the skin and a rise in its temperature was first obtained with novocaine after which from three to five cubic centimeters of

alcohol were injected into each lumbar segment. This was followed in the earlier cases by the injection of a few drops of iodochoral and a roentgen-ray film made to confirm the proper site of injection (figure 8). A hot pack was then applied to the lumbar area for one hour. Most patients were hospitalized for 24 hours, but a few were ambulatory. Of 25 patients, three developed a lasting neuralgia, mostly along the lateral cutaneous nerve of the thigh. All patients develop temporary numbness but this is not often a source of complaints. The sympathetic paralysis lasted from three to six months. In a few cases in which sympathectomy followed the paravertebral injection, no changes in or around the chain and ganglia were noted. The method has a small but definite place in obtaining vasomotor palsy without a two stage major operation; it cannot, however, supplant sympathectomy. For the upper extremity, the stellate ganglion has been repeatedly injected with novocain for diagnostic purposes but very few alcohol injections have been made because of the difficulty of avoiding long lasting and often intractable neuralgias.

Peripheral Nerve Block. The crushing of the sensory nerves of the foot²² has been adopted with a great deal of interest in our clinics. Its use, however, has been gradually diminishing, and we have not done any in the last year. The reasons for abandoning the method were: first, the difficulty of complete desensitization due to many anatomic variations; second, the very painful paresthesias occurring during the period of return of sensation, and third the danger of spreading infection and gangrene since the denervated areas are insensitive and traumatisms are unnoticed and neglected by the patient. Skin areas devoid of sensation lose many of their defensive reactions; the histamine flares cannot be elicited; and though reactive hyperemia following ischemia is obtainable, the hyperemia which follows freezing, scratching, ultraviolet ray or a prick of histamine is absent. The axon reflexes, as shown by Thomas Lewis, are not in operation.²³

Amputations. A detailed study of this material is being prepared by Dr. John Reynolds.* Only a brief summary of his work will be presented here. A total of 34 major and 15 minor amputations has been performed. We have resorted to amputation when (1) parts of the extremity were hopelessly lost and further delay endangered life by absorption of toxic products or spreading infection; and (2) when a cold, pulseless, painful extremity, which was of no possible use to the patient, handicapped his functional recovery and proved to be an economic burden. The optimal level of amputation was determined by the level of adequate circulation and considerations of adequate weight bearing. The cutaneous histamine flares and skin temperature readings almost invariably point to the same level. In arteriosclerotics and diabetics this level is frequently around the knee, although occasionally we have had to amputate at the upper third of the thigh. As Beverly Smith²⁴ has shown, it is possible with a delicate technic to amputate

* de Takats and Reynolds: Amputations in peripheral vascular disease. (To be published.)



FIG. 8. Roentgen-ray film following a paravertebral injection of alcohol followed by a few drops of an opaque substance. Lateral films showed the injections to be well anterior to the intervertebral foramina, thus avoiding as much as possible an injection of the motor and sensory outflow.

7 inches below the knee in certain selected cases and thus save the knee joint. Most of our recent amputations were done with Callander's method²⁵ which in our limited experience has been very satisfactory.

The preparation of the patient consists of diabetic control, improvement of kidney function, if possible, and digitalization in case of cardiac decompensation. This preparation is under the supervision of the Medical Department. To minimize the danger of postoperative gas gangrene, serum for the anaerobic organisms is given in prophylactic doses two to three days prior to operation.²⁶ In a small series, the site of amputation, usually the thigh, was irradiated with a dose advocated for the treatment of gas gangrene.²⁷ A blood transfusion is often remarkably helpful in the handicapped patient. The amputations are done under a low spinal anesthesia with stabilized blood pressure levels obtained by the use of neosynephrine.²⁸ Spinal anesthetics reaching to high levels and lasting two to three hours are avoided and low spinal blocks are obtained with crystalline procaine. In a few patients in whom anesthesia was obtained with pontocaine-glucose, the long lasting depression contributed greatly to their postoperative reactions.

Our mortality was 29.4 per cent.* The causes of death are given in table 9. It can be seen that the majority of patients die of cardiovascular

TABLE IX
Causes of Death Following Amputations
for Peripheral Vascular Disease

	Number of Deaths
Bronchopneumonia	2
Coronary occlusion	2
Delayed shock	1
Cardiac failure	1
Sepsis	4

complications, which is to be expected in such a group. Post-operative infections, especially gas gangrene, however, have been reduced to a minimum with the régime outlined above.

SUMMARY

A brief survey of the methods in use at a group clinic on neurocirculatory diseases has been outlined. In this first communication, peripheral vascular disease has been discussed. A simple classification and a grouping of patients according to various stages of the disease have been presented. The general and local care of the affected extremity have been described.

* This refers only to major amputations; since the use of Callander's technic, pre-operative administration of anaerobic serum and irradiation there was only one death in 10 amputations (10 per cent).

Physical therapy, drug therapy and surgical methods have been discussed and the results of treatment presented.

A combination of these methods is obviously in the best interest of the patient.

BIBLIOGRAPHY

1. WHIPPLE, A. O.: Studies in splenopathy, *Jr. Am. Med. Assoc.*, 1936, cvii, 1775.
2. RAVDIN, J. S.: Personal communication.
3. DE TAKATS, G.: Acute arterial occlusions of the extremities, *Am. Jr. Surg.*, 1936, xxxiii, 60-67.
4. DE TAKATS, G.: Vascular anomalies of the extremities, *Surg., Gynec. and Obst.*, 1932, lv, 227.
5. DE TAKATS, G.: Analysis of results following sympathectomy for peripheral vascular disease, *Am. Jr. Surg.* (In press.)
6. ROSS, P. J.: The recognition of structural changes in the arteries in Raynaud's disease, *St. Barth. Hosp. Rep.*, 1935, cxviii, 121.
7. BECK, WM. C., and DE TAKATS, G.: The use of sodium nitrite for testing the flexibility of the vascular bed, *Am. Heart Jr.*, 1938, xv, 158.
8. DE TAKATS, G.: The differentiation of organic and spastic vascular occlusions, *Ann. Surg.*, 1931, xciv, 321.
9. DE TAKATS, G.: The use of papaverine in acute arterial occlusions, *Jr. Am. Med. Assoc.*, 1936, cvi, 1003.
10. DE TAKATS, G.: Peripheral vascular disease, *Jr. Am. Med. Assoc.*, 1935, civ, 1463.
11. WILDER, R. M., and others: Intake of potassium, important consideration in Addison's disease; metabolic study, *Arch. Int. Med.*, 1937, lx, 367.
12. RABINOWITCH, I. M.: Arteriosclerosis in diabetes: I. The relation between plasma cholesterol and arteriosclerosis: II. Effects of the high carbohydrate low caloric diet, *ANN. INT. MED.*, 1935, viii, 1436.
13. ROSENTHAL, S. R.: Studies in atherosclerosis; chemical, experimental and morphologic; possible dangers of iodine therapy in atherosclerosis of aorta seen from the experimental standpoint, *Arch. Path.*, 1934, cxviii, 824.
14. DE TAKATS, G., HICK, F. K., and COULTER, J. S.: Intermittent venous hyperemia, *Jr. Am. Med. Assoc.*, 1937, cviii, 1951.
15. VEAL, J. R., and McCORD, W. M.: Blood oxygen changes after passive vascular exercise of the extremities, *Proc. Soc. Exper. Biol. and Med.*, 1937, xxxvi, 9.
16. DE TAKATS, G.: Obliterative vascular disease, *Jr. Am. Med. Assoc.*, 1934, ciii, 1920-1924.
17. THIES, A.: Die Behandlung akuter Entzündungen mit rhythmischer Stauung, *Verhandl. d. deutsch. Gesellsch. f. Chir.*, 1913, xlii, 96.
18. ALLEN, E. V., and McKECHNIE, R. E.: The effect of intermittent venous occlusion on the circulation of the extremities, *Jr. Lab. and Clin. Med.*, 1937, xxii, 1260.
19. DE TAKATS, G.: The effect of sympathectomy on peripheral vascular disease, *Surgery*, 1937, ii, 46.
20. DE TAKATS, G.: Sympathectomy for peripheral vascular disease, *Arch. Int. Med.*, 1937, lx, 990.
21. REICHERT, F. L.: Intermittent claudication without gangrene controlled by sympathetic nerve block, *Ann. Surg.*, 1933, xcvii, 503.
22. SMITHWICK, R. H., and WHITE, J. C.: Peripheral nerve block in obliterative vascular disease of the lower extremity. Further experience with alcohol injection or crushing of sensory nerves of lower leg, *Surg., Gynec. and Obst.*, 1935, lx, 1106-1114.
23. LEWIS, T.: Vascular disorders of the limbs, 1936, The MacMillan Co., New York.

24. SMITH, B. C.: Amputation through lower third of leg for diabetic and arteriosclerotic gangrene, *Arch. Surg.*, 1933, xxvii, 267.
25. CALLANDER, C. L.: A new amputation in the lower third of the thigh, *Jr. Am. Med. Assoc.*, 1935, cv, 1746.
26. BATES, M. T.: Gas gangrene; Review of thirty-two cases with special reference to the use of serum, both prophylactic and therapeutic, *Ann. Surg.*, 1937, cv, 257.
27. KELLY, J. F., and DOWELL, D. A.: Present status of x-rays as aid in treatment of gas-gangrene, *Jr. Am. Med. Assoc.*, 1936, cvii, 1114.
28. BRUNNER, R., and DE TAKATS, G.: The use of neosynephrine in spinal anesthesia, *Surg., Gynec. and Obst.*, 1939, lxxviii, 1021.

THE INFLUENCE OF VITAMIN DEFICIENCIES ON OTHER DISEASES *

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It is a popular practice at the present time to give large doses of vitamins in various diseases. Three ideas seem to be the basis of this practice. First, is the belief that a vitamin deficiency may be related etiologically to the disease in question. Second, that the disease may cause or precipitate a deficiency, a so-called "conditioned deficiency." Third, that a preëxisting deficiency or one developing during an illness has an unfavorable effect on the course of the disease in question and that this unfavorable influence can be abolished by relieving the deficiency.

With regard to the first it is interesting that recent studies have failed to show that the lack of a vitamin is responsible for many diseases or disease states other than those already known to be so caused. Certain neuritides are examples of the few exceptions to this fact. With regard to the second a great deal of evidence has accumulated to indicate the importance of many diseases in producing or precipitating vitamin deficiency states, particularly the subclinical or mild forms of these deficiencies. With the current interest and study of the vitamin deficiencies this phase of the problem has overshadowed the third reason mentioned above, namely the effect of the vitamin deficiency on the coexisting disease. Very few adequate studies have been made of this problem.

To the general reader this statement may be rather surprising, for the literature seems to contain many reports of studies of the influence of vitamin deficiencies on disease. On analysis, however, most of them are found to be attempts to establish an etiologic relation between a given vitamin and the disease in question, observations on the effect of treatment on the deficiency alone, or, inadequately controlled and uncritical studies of the *influence* of the vitamin deficiency. The latter have usually consisted only of the administration of large supplements of a vitamin. In many instances there has been no attempt to demonstrate the existence of a deficiency before the vitamin was given. In some cases a deficiency has been inferred from the results of the treatment. In still other cases no consideration at all has been given to the possible existence of a deficiency and the experiment has been in effect a test of the pharmacologic action of the vitamin unrelated to its function as a necessary food factor. Such a procedure is analogous to the use of such an endocrine product as adrenalin as a therapeutic agent without reference to its normal biologic function. Curiously, evidence of such a

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pharmacologic action is unusual in the case of the vitamins, most of which appear to have no effect except in the presence of a deficiency.

It is true that general observations have been made in the past on the influence of such gross deficiencies as scurvy and rickets. Little is actually known, however, with respect to the milder or subclinical deficiencies which are much more common. In part this is due to the greater interest at present in the effect of disease on nutrition. In part it is due to scarcity of suitable clinical methods for discovering the existence of the milder deficiencies.

Because of the wide-spread and uncritical use of vitamins in the treatment of many diseases in the belief that the relief of an *assumed* deficiency would be beneficial and the numerous reports of poorly controlled studies of the effects of the vitamins, it seems worth while to review the state of our knowledge of the influence of vitamin deficiency on disease. In this review I shall refer, for the most part, only to those studies in which reasonable evidence is provided that a deficiency existed and exerted an influence on the disease in question. The omission of other reports will indicate that in general these criteria have not been met. In a few instances I have included studies in which the evidence is less direct. Most of the material deals with human subjects because of the difficulties of transferring results from animal experiments to man in this field. When these stipulations have been met it is surprising how little reliable evidence there is of the effect of vitamin deficiency on disease.

Most of the studies deal with vitamin C deficiency for which fairly satisfactory methods for determining the presence of a mild deficiency have been available for some time. Nevertheless, the number of studies in which a hypovitaminosis C has been satisfactorily demonstrated and reliable observations made of its effect on a disease is disappointingly small. With mild vitamin C deficiency or hypovitaminosis Martin and Heise¹ found in pulmonary tuberculosis that the deficiency of vitamin C paralleled the severity of the disease and the impression was gained that improvement in the tuberculosis was related in part to the relief of the deficiency. In a second paper Heise, Martin and Schwartz² found that 47 per cent of 19 cases of tuberculosis, with a subnormal urinary excretion of vitamin C, showed a significant decrease in sedimentation rate following vitamin C injection. None of five cases with normal vitamin C urinary excretion showed significant changes in sedimentation rate after vitamin C injection. In six controls no alteration in the sedimentation rate was observed during the same period. Radford, et al.³ observed the effect of pure vitamin C, orange juice, and a control product containing no vitamin C, respectively, on about 70 matched cases of tuberculosis over a period of nine months. Observations on the red blood cell count, hemoglobin, lymphocytes, monocyte-lymphocyte ratio, neutrophile-lymphocyte ratio, serum proteins, sedimentation rate, blood fibrinogen and Schilling index, were made at three, six and nine month intervals. At three and six months the groups receiving the pure vitamin C

and the orange juice showed a greater improvement as measured by most of these tests but at the end of nine months some of the advantages of treatment with vitamin C, either pure or in the form of orange juice were lost although these groups still showed superior results in certain respects. Some support to these conclusions is offered by experiments with animals such as those of Greene and his associates.⁴

In diphtheria Otto⁵ found that a group of children found to be on an inadequate intake of vitamin C developed fewer of the hemorrhagic manifestations of the disease when adequate amounts of the vitamin were given though there was no effect on the other aspects of the disease.

Omerod, UnKauf, and White⁶ determined the presence of vitamin C deficiency in a group of children with whooping cough by means of a saturation test. They then gave liberal doses of the vitamin and observed a marked reduction or complete arrest of vomiting, reduction or disappearance of the whoop, reduction in the number and intensity of the day cough in a much shorter time than in a control group. Their study was suggested by that of Otani,⁷ who treated 81 cases with similar results, but did not demonstrate the existence of a deficiency before treatment. Gairdner⁸ has reported a failure to affect the course of whooping cough using the method of Omerod, but Gairdner also failed to test for a deficiency before instituting treatment.

Rinehart,⁹ whose studies deal mainly with vitamin C deficiency as an etiologic factor in rheumatic fever, reported greater gains in weight, better general health and fewer recurrences in spite of intercurrent respiratory infections in a very few patients maintained on an adequate intake of the vitamin compared with controls. Similarly in rheumatoid arthritis,¹⁰ patients in a state of hypovitaminosis C showed considerable improvement when an adequate supply of vitamin C was provided. The capillary resistance test was used to detect and measure the deficiency. In contrast Perry¹¹ measured the state of vitamin C nutrition in cases of active and inactive rheumatic fever and found no correlation between the deficiency and the state of the rheumatic infection. He was, however, more concerned with the etiologic relation of vitamin C to the rheumatic fever.

In pneumonia Bullowa, et al.¹² found a hypovitaminosis C but did not observe much connection between the hypovitaminosis and the course of the pneumonia.

Some of the most valuable studies are those of Ingalls and Warren¹³ and Lanman and Ingalls.¹⁴ These authors observed poor healing and rupture of a surgical incision of the abdomen in a subject who was found to show evidence of latent scurvy at autopsy and a similar occurrence in a second subject who almost surely had a vitamin C deficiency. As the result of these observations they investigated the vitamin C nutrition of 20 patients with peptic ulcer. Ninety per cent were found to have a vitamin C deficiency. Of the 20 patients, eight, all of whom were deficient, had had hemorrhages

and one was one of the subjects who had a rupture of the wound and died following operation. In animal experiments they found that guinea pigs made slightly deficient in vitamin C had poor healing of abdominal surgical wounds and that such wounds ruptured under much less pressure than in normal controls. Archer and Graham¹⁵ similarly found nine patients with ulcer and a vitamin C deficiency but could not come to any conclusion regarding the effect of the deficiency on the healing of the ulcer. However, Payne¹⁶ found that of 51 patients dying following gastrectomy 16 died of peritonitis and of the 16, 12 had leakage at the site of the anastomosis with almost complete absence of a fibrinous response along the suture line. Such a lack of fibrous tissue formation is a characteristic result of vitamin C deficiency.

The high incidence and the severity of infections, particularly respiratory infections, in individuals presenting the more severe manifestations of vitamin A deficiency such as xerophthalmia is well known. Nevertheless in spite of the still rather widely accepted belief that vitamin A is anti-infective and the large amount of this vitamin which is given to patients with respiratory infections there are almost no significant studies of the effect of a mild deficiency on the course of respiratory infections or other diseases.

Many of the studies of the influence of vitamin A deficiency on infections have failed to establish the presence of a deficiency. Others have compared the incidence, or course of infections, in subjects receiving added vitamin with those whose supply was already adequate. Still others have assumed the existence of a deficiency from an analysis of the vitamin content of the liver at autopsy, forgetting that depleted reserves may be the result and not the contributing cause of an infection and that the depleted store is not sufficient evidence of deficiency, the function of the reserve being to carry over a period of increased demand or lowered intake without allowing a deficiency to occur.

Jeghers¹⁷ who used a photometer to detect a deficiency of vitamin A found that a group of medical students who were deficient had had a longer average duration of colds the preceding year than a group who were not deficient. Although the reliability of the photometer test he employed is open to some question the results are probably significant. The study of Shibley and Spies¹⁸ is also very suggestive. Though these authors did not establish definitely the presence of a deficiency preceding treatment they found in a well controlled study of a properly selected group of students a significantly shorter duration of colds among those receiving added vitamin A than in the control groups.

One of the major effects of a deficiency of vitamin B₁ is on the cardiovascular system. This is particularly true of the more severe deficiencies but there is reason to believe that less severe deficiencies exert an influence also. The effect of this deficiency in producing heart disease in the absence of other causes, even in those regions where endemic beriberi is lacking, has

been emphasized recently, particularly by Weiss and Wilkins.¹⁹ It is to be expected that such a deficiency not infrequently complicates a preëxisting heart disease. Malnutrition and cachexia in chronic heart disease are common and well recognized. Such a deficiency may account for some cardiovascular crises, for unexpected congestive failure and for inadequate response to the usual forms of treatment. This possibility is quite generally recognized and has been mentioned by several writers. Yet I have been unable to find any careful and critical study of the effect of mild B₁ deficiencies on other forms of heart disease. Jones and Sure²⁰ observed a general improvement and a better response to treatment in various forms of chronic heart disease in patients given a diet containing more than the usual amounts of B₁ when compared to controls. They did not, however, clearly establish the existence of a deficiency before starting treatment. Although no simple clinical tests for mild B₁ deficiency exist as yet, it is possible to determine with considerable accuracy the adequacy of the vitamin B₁ content of a diet and this, with a careful observation of the early signs and symptoms of the deficiency and a critical use of a therapeutic test with the pure vitamin should make it possible to determine with considerable accuracy the effect of this deficiency on various types of heart disease.

The relation of B₁ to carbohydrate metabolism has aroused interest and a good deal of speculation on the possible influence of vitamin B₁ deficiency on diabetes but there have been no studies reported demonstrating a clear cut and definite effect. Vorhaus, Williams and Waterman²¹ studied carefully 11 diabetics who were given supplements of pure vitamin B₁ for 28 days after a preliminary period of observation. Six showed an increase in carbohydrate utilization, manifested by a drop in blood sugar, a reduction or disappearance of the glycosuria and in some cases a lessened need of insulin. The improvement persisted for a considerable time in four of the six cases. Although some of the subjects may have been deficient in B₁ this was not established in any and there is some uncertainty as to whether the effects observed are to be related to B₁ deficiency as the cause of a diabetic state or to the effect of a vitamin B₁ shortage on the ordinary type of diabetes.

While there is little reason to doubt that mild or subclinical pellagra has an effect on the course of other illness there is no specific information about it. This may be attributed to the fact that no good clinical test for this hypovitaminosis exists and in the presence of established pellagra interest has settled on it rather than on associated diseases.

From this review it is apparent that there is little reliable scientific evidence of the effect of vitamin deficiencies on disease and hence little justification on these grounds for the current wide-spread use of vitamins as therapeutic agents in a great number of illnesses. This does not mean that such an influence is lacking or that one would neglect the presence of deficiencies and fail to employ such measures as are needed to insure ade-

quate nutrition. On the contrary there is good reason to believe vitamin deficiencies occur as complications of many diseases and modify unfavorably their course and outcome. For the present, however, with few exceptions, the influence of vitamin deficiencies must be considered to be that which might reasonably be expected of a poor nutrition generally, without reference to specific and clearly demonstrated effects. It is to be hoped that with the present rapid development of methods for determining the existence of specific deficiencies of a mild character their effect on various diseases will be determined. Through these methods there is opened up a great opportunity for careful, critical, clinical research of great importance. Only on the basis of such research with patients can the effect of these deficiencies and the value of treatment with the specific substances be determined in human subjects.

BIBLIOGRAPHY

1. MARTIN, GUSTAV J., and HEISE, FRED H.: Vitamin C nutrition in pulmonary tuberculosis, *Am. Jr. Digest. Dis. and Nutr.*, 1937-38, iv, 368.
2. HEISE, FRED H., MARTIN, GUSTAV J., and SCHWARTZ, SPENCER: The influence of the administration of vitamin C on blood sedimentation and sensitivity to tuberculin, *Brit. Jr. Tuberc.*, 1937, xxxi, 23.
3. RADFORD, MOLLY, DE SAVITSCH, EUGENE, AND SWEANY, HENRY C.: Blood changes following continuous daily administration of vitamin C and orange juice to tuberculous patients, *Am. Rev. Tuberc.*, 1937, xxxv, 784.
4. GREENE, MERIDIAN R., STINER, MORRIS, and KRAMER, BENJAMIN: The rôle of chronic vitamin C deficiency in the pathogenesis of tuberculosis in the guinea pig, *Am. Rev. Tuberc.*, 1936, xxxiii, 585.
5. OTTO, HANS: Die Behandlung der Diphtherie mit Ascorbinsäure, *Klin. Wchnschr.*, 1936, xv, 1510.
6. OMEROD, M. J., UNKAUF, BYRON M., and WHITE, F. D.: A further report on the ascorbic acid treatment of whooping cough, *Canad. Med. Assoc. Jr.*, 1937, xxxvii, 268.
7. OTANI, T.: Über die Vitamin C-Therapie des Keuchhustens, *Klin. Wchnschr.*, 1936, xv, 1884.
8. GAIRDNER, DOUGLAS: Vitamin C in the treatment of whooping cough, *Brit. Med. Jr.*, 1938, ii, 742.
9. RINEHART, JAMES F.: Studies relating vitamin C deficiency to rheumatic fever and rheumatoid arthritis; experimental, clinical, and general considerations. I. Rheumatic fever, *ANN. INT. MED.*, 1935-36, ix, 586.
10. RINEHART, JAMES F.: Studies relating vitamin C deficiency to rheumatic fever and rheumatoid arthritis; experimental, clinical and general considerations. II. Rheumatoid (atrophic) arthritis, *ANN. INT. MED.*, 1935-36, ix, 671.
11. PERRY, C. B.: Rheumatic heart disease and vitamin C, *Lancet*, 1935, ii, 426.
12. BULLOWA, JESSE G. M., ROTHSTEIN, ISIDORE A., RATISH, HERMAN D., and HARDE, EDNA: Cevitamic acid excretion in pneumonias and some other pathological conditions, *Proc. Soc. Exper. Biol. and Med.*, 1936, xxxiv, 1.
13. INGALLS, T. H., and WARREN, H. A.: Asymptomatic scurvy: its relation to wound healing and its incidence in patients with peptic ulcer, *New England Jr. Med.*, 1937, ccxvii, 443.
14. LANMAN, THOMAS H., and INGALLS, THEODORE H.: Vitamin C deficiency and wound healing. An experimental and clinical study, *Ann. Surg.*, 1937, cv, 616.

15. ARCHER, H. E., and GRAHAM, GEORGE: The subscurvy state in relation to gastric and duodenal ulcer, *Lancet*, 1936, ii, 364.
16. PAYNE, REGINALD T.: The post-mortem findings after partial gastrectomy, *St. Barth. Hosp. Rep.*, 1936, lix, 191.
17. JEGHERS, HAROLD: The degree and prevalence of vitamin A deficiency in adults. With a note on its experimental production in human beings, *Jr. Am. Med. Assoc.*, 1937, cix, 756.
18. SHIBLEY, GERALD S., and SPIES, TOM D.: The effect of vitamin A on the common cold, *Jr. Am. Med. Assoc.*, 1934, ciii, 2021.
19. WEISS, SOMA, and WILKINS, ROBERT W.: The nature of the cardiovascular disturbances in nutritional deficiency states (beriberi), *ANN. INT. MED.*, 1937-38, xi, 104.
20. JONES, WILLIAM A., and SURE, BARNETT: The rôle of vitamin B₁ in cardiovascular diseases, *Jr. Lab. and Clin. Med.*, 1936-37, xxii, 991.
21. VORHAUS, MARTIN G., WILLIAMS, ROBERT R., and WATERMAN, ROBERT E.: Studies on crystalline vitamin B₁: observations in diabetes, *Am. Jr. Digest. Dis. and Nutr.*, 1935-36, ii, 541.

EXPERIMENTAL AND CLINICAL OBSERVATIONS RELATING TO THE MANAGEMENT OF ACUTE BOWEL OBSTRUCTIONS *

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It is not so long ago that the depth of a lesion beneath the body surface determined whether the malady was surgical or medical in character. Externists or surgeons concerned themselves with the practical affairs of setting bones and the treatment of ulcers, wounds and ailments of the body surface. The problems of the less pragmatic but more erudite internists centered about internal disorders. The surgeon chanced an occasional excursion beyond his frontiers, but save for the management of vesical calculi, rarely did these meanderings redound to his honor or that of his guild. Anesthesia, antiseptics and the discovery of the new science of bacteriology changed all this.

The venturesome surgeon would no longer suffer the epithet of externist. He embarked on a course of aggrandizement and by strategy of force attempted the annexation of strange territories. In some fields, for example that of goiter, a successful 'Anschluss' was readily made. Victories, costly in life and prestige, soon taught the intransigent surgeon the value of compromise—a virtue which is still observed to come with a more natural grace from internists than from those who trace their professional ancestry back to externists. The externists have made minor concessions also and diseases of the skin have been ceded to the internists.

Though the surgeon professes to be his own internist in certain provinces, in the main, he has learned that his life is less fitful if he does not wander too far afield from his more complacent companion. The very nature of the surgeon's work, however, does not permit him to enjoy the tranquillity of mind, even when he attempts to imitate the serenity of his brother with a greater traditional culture of learning. If any of the stigma of step-child relationship attaches still to the kinship between surgeon and internist, the surgeon puffed up with the knowledge of what his art has done for the science of medicine is too proud to admit any slight.

To Which Province Does Bowel Obstruction Belong? One of the early skirmishes between physician and surgeon concerning abdominal ills was fought over the management of bowel obstruction. At the first joint congress of the American Association of Physicians and Surgeons held in 1888, the subject of bowel obstruction was one of the chief topics of debate. The medical point of view was presented by Reginald Fitz⁵ and the surgical by

* Read at the New Orleans meeting of the American College of Physicians March 30, 1939.

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Supported by a grant from the Graduate School of the University of Minnesota, and also by a grant for technical assistance by the Federal Public Works Administration, Project No. 665-71-3-69, Sub-project No. 258.

Nicholas Senn.⁷ The mortalities in both hands were practically identical—between 69 and 70 per cent. The consensus of opinion seemed to be, nevertheless, that after trial with conservative measures for two days, recourse should be had to surgery. The following year, just 50 years ago now, before the German Congress of Internists convened at Wiesbaden, Professor Curschmann⁸ deplored the bad results of surgical treatment and stated that medical measures gave fully as large a number of recoveries. In his clinic, the mortality of the conservative management of bowel obstruction was 65 per cent.

Despite the poor accomplishment of the surgeon, the physician recognized the futility of treating mechanical interruption of intestinal continuity by conservative means and surrendered the field to his competitor. Ten years later (1899) the late Sir Frederick Treves,⁸ in his day a recognized authority in the field of bowel obstruction, said: "Those who are enamoured of statistics could, I have little doubt, show that it is less dangerous to leap from the Clifton Suspension Bridge than to suffer from acute intestinal obstruction and decline operation." That it was almost equally as hazardous to jump into the therapeutic net of the surgeon, a number of statistical studies showed. Whereas here and there a surgeon exhibited skill above the ordinary in aiding patients afflicted with intestinal occlusion to safety, in the main the risks were large. As late as 1929, the late C. Jeff Miller⁶ of New Orleans found that the mortality of acute bowel obstruction in the Touro Infirmary and the Charity Hospital was 60.9 per cent—certainly no great improvement upon the results obtained in those days when it was debated whether obstruction was a medical or surgical malady.

Since then, even surgeons have reverted to non-operative means of relieving certain types of bowel occlusion of mechanical origin and have found the method useful.

The Management of Acute Intestinal Obstruction. In essaying to discuss the treatment of intestinal obstruction, I am appearing before you essentially in the rôle of preacher rather than teacher. For in a strict sense, teachers strive to impart new knowledge not possessed before, while the function of a preacher is to attempt to lend meaning to knowledge which the learner possesses already.

Intelligent management of occlusion of the bowel rests upon three factors: (1) knowledge of the effects of obstruction; (2) acquaintance with dependable diagnostic criteria by which its presence may be recognized; and (3) an appreciation of the value of therapeutic agencies in the relief of obstruction.

The Effects of Obstruction. These are essentially of two kinds: (1) effects upon the organism as a whole, and (2) the effects of obstruction upon the bowel wall.

Whereas the number of clinical varieties of obstruction is large, from a pathological standpoint there are essentially two kinds: (1) simple, and (2) strangulating obstructions. Simple obstruction exhibits interruption of in-

testinal continuity only; in strangulating obstruction involvement of the blood supply is present as well. In addition to the pathological type of obstruction present, another important determinant of symptoms as well as of effects of intestinal obstruction is the site of occlusion.

Up until almost as recently as a decade ago it was held quite generally that the absorption of lethal toxins from the lumen of the obstructed bowel was the most significant among lethal factors in causing death in intestinal obstruction. Experimental and clinical observations of the past 15 years have changed all this. The mechanical effects of distention upon the bowel wall, the loss of fluid and electrolytes by vomiting and the loss of blood in strangulating obstructions are becoming more generally recognized as the agencies through which the mischievous effects of bowel obstruction are mediated.

The Avenues for Absorption. The normal avenue of absorption from the bowel is the mesenteric pedicle and absorption occurs either via the portal circulation or through mesenteric lymph radicles which reach the *cisterna chyli*. In late obstructions, however, a new avenue is opened up, namely, the transperitoneal migration of noxious substances. When the viability of the bowel wall has been impaired by long sustained increases of intraluminal tension or the flow of blood from or to the bowel has been arrested by agents such as torsion or obstruction of its blood vessels, the mucosa of the obstructed bowel becomes permeable to substances to which the normal bowel wall is impermeable.

The Intraluminal Pressure in Bowel Obstruction. Determinations of the sustained intraluminal pressure in the obstructed gut have been made in man and in experimental animals. In the obstructed small bowel of man sustained intraluminal pressures varying between 4 and 14 centimeters of water were noted with occasional rises to 20 or 30 centimeters. In the dog, varying fairly directly with the duration of the obstruction, sustained pressures of 4 to 19 centimeters of water were observed. In a number of dogs pressures were determined by puncture through Biebl loops, segments of exteriorized gut covered with skin, presenting the appearance of a "satchel handle." The pressures determined in this manner were of the same order of magnitude as those determined in the dog after opening the abdomen. The observed pressures recorded here for man were made after the abdomen had been opened and closed and only after the withdrawal of a few cubic centimeters of gas from an intestinal loop segregated between two intestinal clamps to permit performance of an aseptic enterostomy. Such small withdrawals in an elastic cylinder like the gut, within the range of pressures herein described, do not affect significantly the end pressures.

In the obstructed colon in man, a higher order of pressures is observed, for the colon when obstructed becomes essentially a closed loop into which the gas and fluid from the small intestine continue to be evacuated, while regurgitation back into the ileum is precluded by the lips of the ileocecal

valve and sphincter. In patients with great distention, intracolonic pressures in excess of 20 centimeters are the rule.

Summary of Systemic Effects of Obstruction. In high obstructions in which vomiting is a prominent feature, the loss of fluid is usually great. It has been estimated that the digestive juices (saliva, gastric juice, bile, pancreatic juice and succus entericus) dumped in at the gateway of the intestinal canal approximate 7000 c.c. a day. Repeated regurgitant vomiting copious in amount brings about dehydration as well as dechlorination. When these end effects have become manifest they are heralded by the presence of alkalosis, a low blood chloride value and abnormal retention of non-protein nitrogen in the blood.

In strangulating obstructions the blood loss factor may be great, owing to prevention of egress of blood from the mesenteric vessels, and to the continued arrival of blood in the intestine under the motive force of systolic blood pressure. A dog, in which the veins to a segment of bowel two feet in length have been tied, will die of hemorrhage in about four hours. If the portal vein is tied, bleeding into the gut will cause death in about an hour's time. Ligation of the arterial supply of a segment of gut, on the contrary, is survived for 16 to 20 hours—until the bowel wall has permitted transudation of noxious substances.

Determinations of venous pressure in the lower extremities in patients with great intestinal distention indicate that definite increases over the normal are observed.² The circulation time is slowed as well (table 1). In

TABLE I

Venous Pressure (Ankle Vein) and Circulation Time (Ankle Vein to Carotid Sinus by Sodium Cyanide Method) in Patients with Clinical Intestinal Distention

Case	Venous Pressure Ankle Cm. Water	Circulation Time	
		Cubital- Carotid Seconds	Ankle Vein to Carotid Seconds
1. E. R. #664078, M 55 ^a	12	20	52
2. A. H. #665956, M 69 ^b	15.5	19	No response in horizontal. 22" in Trendelenburg * 30°
3. A. R. #666676, M 53 ^c	17.5	18	No response in horizontal. 15" in Trendelenburg * 30°
4. J. S. #657879, M 70 ^d	3	22	35
5. R. W. #664244, M 62 ^e	29	12	49

^a Carcinoma of pelyic colon with acute obstruction—pressure at operation 20 cm. water, 1800 c.c. gas aspirated.

^b Carcinoma of pelvic colon—pressure at operation 15 cm. water, 1500 c.c. gas aspirated.

^c Carcinoma of stomach with distention owing to metastases.

^d Mass in terminal ileum treated conservatively by suction; five days later, ileostomy—intraluminal pressure 14 cm. water, 600 c.c. gas and fluid aspirated at operation.

^e Abdominal injury with marked intestinal distention treated conservatively by suction applied to indwelling duodenal tube.

* Downward inclination.

TABLE II

Relation between Intraluminal, Intraperitoneal, Femoral Vein (or Saphenous), Inferior Vena Cava, Carotid Artery (or Femoral Artery), and Portal Vein Pressures in Distended Dogs (Bowel Inflated with Air). First Figure Indicates Initial Reading; the Second, the Resultant Reading

Dog	Duration of Experiment	Amount of Air Injected c.c.	Systolic Arterial Blood Pressure mm. Hg	Intraluminal in Gut Cm. Water	Intraperitoneal Pr. Cm. Water	Femoral or Saphenous Vein Cm. Water	Inferior Vena Cava Cm. Water	Portal Vein Cm. Water
1	1 hr. 55 min.	2600	120 60	0 100	0 10	3 43	8 (Through divided renal vein)	—
2	2 hr. 25 min.	3200	100 60	0 202	0 18	10 31+	4 2 0 (Through divided renal vein)	—
3	6 hr.	—	135 shock	0 100	0 10	7 21+	3 8 (Through catheter in femoral vein)	—
4	6 hr.	—	144 162	0 50	0	5	2 (Through catheter in femoral vein)	14 17 7 (Through divided inferior mesenteric vein)
5	8 hr. 30 min.	2250	110 shock	0 30	0 9	10 15	7 (Through catheter in femoral vein)	18 4 (Through divided splenic vein)
6	8 hr. 15 min.	—	110 65	0 50	3 4	5 11	6 (Through catheter in femoral vein)	17 26 8 (T-tube in portal vein)

dogs in which the bowel was inflated with air after obstructing the terminal pelvic colon, it was noted that the rises in the venous pressure of the lower extremities attending the distention exceeded the vena caval and portal pressures (table 2). As a matter of fact, the venous pressure in the portal vein falls coincidentally with the establishment of tense intraluminal distention, due to the diminution of outflow of blood from the bowel (table 3). It is

TABLE III

Relation of Intraluminal Pressure in Bowel of Dogs to Mesenteric Venous Pressure Attending Inflation of Gut with Air

Intraluminal Pressure Cm. Water	Mesenteric Venous Pressure Cm. Water
0	13
10	12
20	12
30	12
40	10
50	6
60	5.5
70	5
80	5
90	6
100	6

to be remembered that normally the portal venous pressure is high as compared with the venous pressure at heart level in the systemic veins, because the portal venous blood still has to flow through the hepatic capillaries. These observations indicate that simple obstruction alone when attended by distention of high grade may also be a factor in the production of shock—a common accompaniment of strangulating obstructions owing to blood loss into the infarcted segment.

The Local Effects of Obstruction. The effect of obstruction upon the gut is in part easy to determine and in part very difficult. When the nature of the obstruction is such that arrest of outflow of blood is occasioned, it is apparent that infarction of the gut will ensue with loss of blood as described above and also by impaired viability and increased permeability. This latter occurrence may be occasioned also by great increases of intraluminal distention alone and is noted particularly in colonic obstruction as described above. Even in low long-continued ileal obstructions, in which vomiting has failed to drain the bowel and lower the intra-enteric pressure, impaired viability of the gut follows, though by no means as quickly as in colonic obstructions or in strangulating mechanisms in which the blood supply is obviously damaged.

When the digestive juices referred to above descend into the obstructed gut, from which the absorption of water is seriously diminished as contrasted with the normal, it is apparent that the gut will distend. In addition, however, to the alimentary fluids, there is the intestinal gas, derived in large part from swallowing of air. It is the experience of all clinicians who have given

the matter any notice that it is largely gas that distends the bowel in acute obstructions of short duration. How significant this item of gaseous distention may be is indicated by exclusion of the swallowed air factor by esophagostomy in ileal obstructions which type of experiment may be survived for as long as 57 days—the dog dying of starvation.¹² When swallowed air is excluded, the obstructed intestine of the dog will usually absorb all the digestive juices dumped into it, and when the animal dies the bowel is not distended. It is more than likely that the same will occur in man, whose small intestine possesses an absorptive area greater in length than that of the dog.

In high obstructions, in which vomiting empties the distended loops, increases of intraluminal tension are not long sustained. Even relatively low grades of pressure, like the upper values observed in obstruction of the small intestine of man or the dog, when unrelieved over a period of days, will result in injury of the intestinal wall, permitting transperitoneal migration of injurious agents.

The Recognition of Obstruction. Fundamental for the detection of the presence of obstruction, as well as its intelligent management, is recognition of the differential characteristics of simple and strangulating obstructions and of the essential differences in many of the symptoms of obstruction of the large as contrasted with the small bowel. *Intestinal colic* is the pathognomonic finding of all obstructions, indicated by the presence of concurrent intestinal noises or borborygmi coincident with recurrent intermittent crampy pains which the patient describes as “gas pains.” True enough, such *intestinal colic* may attend dietary indiscretions, allergic reactions due to food, or enterocolitis, but on the basis of general symptoms these conditions may be excluded.

Is the Obstruction Simple or Strangulating in Type? Simple obstruction is unattended by abdominal tenderness and is characterized only by *intestinal colic*. Strangulating obstructions have to be differentiated from all conditions which cause tenderness of the abdominal wall (which means most acute abdominal disorders). The pathognomonic finding of *intestinal colic* serves to differentiate. Only in those acute inflammatory lesions in which exudate causes arrest of intestinal continuity does difficulty in differentiation arise. It is to be conceded freely that this distinction at times can not be made absolutely without recourse to operative intervention. In late simple obstruction, in which sustained increases of intraluminal pressure have been present for two days or more, the gut may “weep.” As a result of this sudden transudation of fluid into the peritoneal cavity, the peritoneum, the most sensitive of all serous membranes, exhibits “rebound tenderness” occasionally—an indication that something has escaped into it.

One of the difficulties which hedges about the recognition of strangulating obstructions which are first observed, only after the lapse of some time, is the lack of active peristaltic activity. *Intestinal colic* is, therefore, frequently not a prominent feature in late strangulating obstructions, peristaltic

activity being inhibited in part by the escape of sanguineous fluid into the peritoneal cavity. Yet auscultation of the patient's abdomen over long intervals of time will usually serve to identify the presence of *intestinal colic*. Careful attention to the details of the history helps considerably in orienting the observer.

Is the Obstruction in the Small or Large Intestine? The distinction between obstructions of the small and large intestine can often be made on clinical evidence. In the former, repeated vomiting, often copious in amount, is the rule—contingent in part, of course, on the grade of obstruction present. Stercoraceous or feculent vomit is characteristic of obstructions of the lower ileum. In obstructions of the colon, on the contrary, vomiting is often absent altogether. Reflex vomiting may occur initially as it may with any abdominal colic. The absence or presence of vomiting in obstructions of the colon hinges upon the occurrence of regurgitation from the colon into the ileum, which in turn depends upon the length of the lips of the ileocecal valve. When one of these is deficient in length (the inferior, usually) such regurgitation may occur. In the experience of the writer, however, the competency of the ileocecal valve and sphincter is the rule, though it is to be admitted freely that exceptions do occur. Over an interval of nine years during which time the writer has been alive to a difference in the manifestations of obstructions of the large and small bowel, eight cases of perforation of the colon during the course of obstruction have come under his observation, brought about by competency of the ileocecal valve and sphincter.

Patients with colonic obstruction not only may fail to vomit, but gastric aspiration in such cases demonstrates almost invariably the absence of gastric retention. Only gastric juice or air is aspirated usually from the stomach, whereas in obstruction of the small bowel, the aspirations are often large in amount and frequently brown in color, significant of the presence of stasis in the small bowel. The bottles used for collecting the fluid aspirated from the stomach should, therefore, be transparent so that this important item may be noted with accuracy.

The Value of the Roentgen Film. The roentgen film reveals significant information concerning two important particulars: (1) where the distended intestinal coils are, and (2) the extent of that distention.

Whether the colon or the small intestine is distended can be determined usually without difficulty. There are times, however, when it is by no means easy to decide which is distended. The basis of this differentiation has been described previously and will not be repeated here. The size of the distended coils, bearing in mind the diffraction of the roentgen-rays and the enlargement of the image (usually about 25 per cent of an object within the peritoneal cavity, with the patient supine), gives helpful information in determining whether the obstruction is complete or incomplete and whether the distention is of such a grade as to threaten the viability of the bowel wall.

The value of the roentgen findings cannot be overestimated when correlated intimately with the clinical findings. To recommend therapy or employ it without recourse to roentgen examination is to neglect an important source of information. Yet, interpretations reported by the roentgenologist without knowledge of the clinical status may be very misleading. Roentgenologists, on the basis of their source of evidence alone, diagnose obstruction not uncommonly when it does not exist.

Enemas. Enemas are of no value in determining whether obstruction is present. Their chief worth lies in ascertaining whether obstruction in the small bowel is complete or not. If a patient has had evacuant enemas and a roentgen-ray film indicates that gas is still present in the colon, it indicates that gas has succeeded in getting past the obstructive lesion.

Identification of the Obstruction. In résumé one may say that the presence of *intestinal colic* in correlation with other attendant symptoms or physical signs enables one to say that bowel obstruction has occurred. The absence or presence of rebound tenderness determines whether the obstruction is simple or strangulating in nature. Whether the obstruction is in the small intestine or colon can be stated with surprising accuracy on the basis of the absence or presence of vomiting and by the absence or presence of intestinal fluid in the gastric aspirations. The return of a brownish feculent-like material indicates that the obstruction is in the small bowel. In colonic obstructions, gastric fluid, occasionally tinged with bile and air constitutes the return; occasionally, there may be no return. Roentgen-ray observations lend helpful confirmatory evidence. Whether the obstruction is complete or partial may be determined by the extent of the distention in part; and in obstructions of the small intestine the persistence or absence of gas in the colon after evacuant enemas* helps to decide.

TREATMENT

Strangulating Obstructions. The problem of management of bowel obstruction is an interlocking one between diagnosis and choice of operative procedure. Every patient with a strangulating obstruction should be operated upon at once. The time element looms large in all obstructions of this variety. For, with the single exception of thrombosis or embolism of the mesenteric vessels, all strangulating obstructions, if operated upon early, may be treated as instances of simple obstruction. If the blood supply has been interrupted beyond the interval of spontaneous recovery of the gut with restoration of blood flow, the gut must be removed. The return of a normal color to the gut and pulsation in the vessels are the surgeon's chief guides in determining whether the intestine should be excised or left undisturbed. In cases of dubious viability of the bowel, the surgeon may exteriorize it in continuity upon the abdominal wall; if viable it may be returned safely later. Whereas surgeons have, in the main, considered it hazardous to do primary

* Enemas must not be given in the presence of an inflammatory intraperitoneal lesion for fear of disseminating the infection.

resections save in selected instances of non-viable bowel for strangulating obstructions, with more general adoption of aseptic methods of anastomosis, it may prove that primary resection is equally as safe and a much preferable procedure to fistulization.

However valuable other agents of therapy may be, every one is in accord that all patients having strangulating obstructions should be submitted to early operation. The devitalized bowel brooks no delay.

Simple Obstruction. It is in this variety of obstruction that the efficacy of various remedial agents can be best evaluated. It should be emphasized that operation constitutes still the most important agent in the relief of obstruction. In simple obstruction, the operation of election (release of the obstructing mechanism) should be confined to early cases. In all late cases the compromise procedure of decompression (enterostomy) will save many more lives. The evisceration and manipulation of a distended bowel with threatened loss of viability from long sustained increases of intraluminal tension cannot be accomplished without risk. Further, the removal of ensnaring adhesions which have become agglutinated to the gut is a hazardous undertaking which invites spillage and disaster. In such instances an *aseptic* decompression or drainage of the bowel will usually bring relief. In adhesive types of obstruction, the continuity of the bowel will usually be established automatically by this procedure alone. It is to be freely admitted that there is a mortality of treatment as well as of disease. Only operative procedures which are accomplished aseptically can be done with little risk.

CONSERVATIVE THERAPEUTIC MEASURES

Saline Solution. It has been indicated that the virtue of saline solution lies in its ability to restore a disturbed electrolyte balance and to combat dehydration. In all high obstructions in which vomiting is a prominent feature and in which dehydration and loss of electrolytes obtain, saline solution may improve the patient's status in the same measure as pouring water on a withering flower. Such a measure accomplishes nothing, however, for the relief of the obstruction; it merely improves the condition of the patient to tolerate what needs to be done to reestablish intestinal continuity. In patients with low obstruction (colonic) in which vomiting may be absent altogether, saline solution is in no sense the specific revitalizer that it is for high obstructions.

Transfusion of Blood. In all strangulating obstructions in which the imprisoned segment of bowel is long, the loss of blood may be great. This situation is heralded by a hurried pulse and a blood pressure which hovers around the critical clinical level, 100 to 110 mm. Hg.* A quickened pulse unrelieved by the administration of saline solution in a patient who exhibits the signs of a strangulating obstruction (*intestinal colic* plus rebound ab-

* The 70 to 80 mm. Hg critical level spoken of by the physiologists relates to a situation in which the vital centers are threatened if the level of systolic pressure is not elevated. It is far safer for surgical house officers to consider the critical level to lie between 100 to 110 mm. Hg for pre- as well as postoperative patients.

dominal tenderness) is an absolute indication for the transfusion of blood. A patient with intussusception may bleed to death into the infarcted gut. It is startling to observe what transfusion may do for such a patient.

It has been indicated also that the presence of great distention may retard the return flow of blood from the lower extremities. Employment of the Trendelenburg position to facilitate drainage of venous blood from the lower extremities is, therefore, in order.

Oxygen. The inhalation of high concentrations of oxygen, as suggested by Fine⁴ and his associates, does encourage the migration of nitrogen from the bowel. Swallowed air, the chief source of gas in the distended bowel, does not leave the bowel ordinarily in appreciable quantities because of the high partial pressure of nitrogen in the plasma. When the tension of nitrogen in the plasma is reduced to a low level by exclusion of nitrogen in the inspired gas the diffusion of nitrogen from the distended gut is encouraged. This measure should be looked upon as an adjunct means of aiding deflation rather than as a direct attack upon the obstructing mechanism.

Conservative Decompression. Since the effectiveness of decompression in accomplishing relief of distention in certain types of acute mechanical obstruction was demonstrated in 1931,⁹ this method has come to be widely employed, largely as an ancillary mode of aiding deflation. The absolute contraindications (strangulating obstructions and obstructions of the colon with great distention), the indications, as well as the relative indications and contraindications were pointed out in 1931. These have remained essentially the same. Accepting published literature on the subject as an indication of the extent to which suction applied to an inlying duodenal tube is employed in the management of simple bowel obstruction, one gathers the impression quite definitely that it is regarded essentially as an adjunct agent, being valuable in the pre- as well as postoperative management. The published experience of a few clinics with its use would indicate, however, that by its use alone, not infrequently, decompression may be achieved in certain types of mechanical obstruction.

The item of accurate diagnosis, the use of frequent bed-side films, and the willingness on the part of house officers to spend hours diligently aiding the progress of the tube into the gut are requisites, without which the method cannot often succeed. One cannot put a tube into the stomach and come back after the lapse of four to six hours and expect decompression to have occurred. Though even this may happen! That the method has virtue is evidenced by the low mortality rate in the group of cases in which decompression is achieved by this method (tables 4, 5 and 6).¹¹ An undesirable feature of the method is that one does not succeed in decompressing, by any means, all cases in which its use is tried. It is not difficult to understand that through the use of decompression operation may be deferred until the patient is an even worse risk for operative intervention than he was initially. The possibility of this error in judgment is the chief hazard of the method provided that initially it is used only in suitable cases. If suction is used

with discretion and the clinician three or four times a day resurveys the situation from the standpoint of the patient's condition and the findings in films of the abdomen the writer has the impression that this conservative regimen is fully justified.¹⁰ The writer is convinced from his own ex-

TABLE IV

Summary of Mortality of Cases of Acute Mechanical Obstruction of Small Intestine Treated at University Hospital between June 1, 1931 and June 1, 1938

	Number	Number of Deaths Related to Obstruction	Per cent Mortality
All treated cases:			
Total mortality by patients	156	28	17.9
Total mortality by cases	190	28	14.7
All cases treated by suction:			
Total mortality by patients	96	15	15.6
Total mortality by cases	126	15	11.9
Cases decompressed by suction:			
Total mortality by patients	64	5	7.8
Total mortality by cases	83	5	6.0

TABLE V

Division of Cases and Mode of Management with Mortality

	Number of			Per cent Mortality		Unrelated Deaths	Corrected Per cent Mortality	
	Patients	Cases	Deaths	Patient	Case		Patient	Case
GROUP I. The Suction Group								
A ¹	57	66	10	17.5	15.1	6	7.0	6.0
B ²	17	17	1	5.9	5.9	0	5.9	5.9
C ³	38	43	14	36.8	32.6	4	26.3	23.3
GROUP II. Patients treated by immediate op- eration								
A ⁴	5	6	2	40.0	33.3	1	20.0	16.6
B ⁵	45	47	9	20.0	19.1	0	20.0	19.1
C ⁶	15	15	6	40.0	40.0	0	40.0	40.0
GROUP III. Miscellaneous Group ⁷	16	16	6	37.5	37.5	1	33.3	33.3

¹ Patients in whom suction applied to an inlying duodenal tube was the only treatment directed at the relief of the obstruction (no operation).

² Patients decompressed by suction but operated upon subsequently because of demonstrated or conjectured persistence of obstructive mechanism.

³ Patients in whom suction was unsuccessful in effecting decompression and in whom operation became necessary for satisfactory relief from acute obstruction.

⁴ Intraperitoneal obstructions.

⁵ Strangulated or incarcerated hernias.

⁶ Intussusception—several late cases in this group.

⁷ A miscellaneous group in which no therapy directed at the relief of obstruction was carried out because: the patient was moribund or dead on arrival at the ward; the obstruction had righted itself spontaneously; or the presence of obstruction was not recognized.

TABLE VI
Per cent of Patients Treated by Suction Alone

	Patients	Cases
GROUP I. The Suction Group		
A. Patients in whom suction applied to an inlying duodenal tube was the only treatment directed at the relief of the obstruction (no operation)	36.5%	34.7%
B. Patients decompressed by suction but operated upon subsequently because of demonstrated or conjectured persistence of obstructive mechanism	10.9%	8.9%
C. Patients in whom suction was unsuccessful in effecting decompression and in whom operation became necessary for satisfactory relief from acute obstruction	24.4%	22.6%
Total patients decompressed by suction only—47.4%		
Total cases decompressed by suction only—43.6%		

perience that *aseptic* operative decompression in late cases of simple obstruction can be accomplished without great risk, granted that the transperitoneal route of absorption has not been opened up by long sustained rises of intraluminal pressure which have vitiated the viability of the gut wall.

The Miller-Abbott¹ tube is undoubtedly a distinct improvement in encouraging migration of the tube down the gut. In the experience of this clinic, however, the indications for the suction method in the management of mechanical obstruction have not been increased by its use.

It need scarcely be added that fluid must be restored by para-oral routes, in amounts adequate to cover both the ordinary fluid and mineral requirement of the body as well as the amount recovered by aspiration from the intestinal canal.

Lessons Taught by Suction. The wide use of suction in the management of distentions of many types has constituted a means of learning the behavior of conditions, previously not well understood. It has taught us that distention of the stomach and upper reaches of the bowel is the chief cause of postoperative vomiting. Clinicians have learned that distention may be prophylactically avoided by early employment of suction after operation to remove swallowed air and increments of fluid which accumulate in the upper reaches of the gastrointestinal canal and that the prevention of postoperative distention does away practically with the early postoperative mechanical obstructions. It has taught us also that patients die of peritonitis from peritoneal infection and that relieving distention may not alter the situation.

SUMMARY

The intelligent management of bowel obstruction envisages an understanding of the effects of obstruction, its recognition, and an accurate appraisal of the true value of therapeutic agents.

A careful coördination of clinical and roentgen findings will usually indicate with accuracy: (1) whether obstruction is present; (2) whether it is

simple or strangulating in character; (3) where the obstruction is; (4) whether the obstruction is complete or incomplete. Unfortunately the exact variety of obstruction and the manner in which the bowel is obstructed may not be disclosed without operative intervention and even then its precise nature may remain somewhat in doubt.

The old axiom that the high obstructions are the most serious should be altered. Low obstructions hold far greater risk to life in that sustained intraluminal pressures threaten the viability of the bowel wall. Vomiting obviates this occurrence in high obstructions and the fluid and mineral loss can be replaced simply by free administration of saline solution. All low obstructions need early decompression of the bowel to maintain a normal blood flow. Blood loss is a factor to be reckoned with in all strangulating obstructions.

Saline solution, transfusion of blood, and oxygen are adjunct measures of treatment, all of which have their indications. The direct measures of relief are operation and suction applied to an indwelling duodenal tube. Operation is still the most dependable agent in the relief of mechanical obstructions, but suction renders operation unnecessary in certain types of cases.

REFERENCES

1. ABBOTT, W. O., and JOHNSTON, C. G.: Intubation studies of the human small intestine, *Surg., Gynec. and Obst.*, 1938, lxvi, 691-697.
2. BELLIS, CARROLL J., and WANGENSTEEN, OWEN H.: Unpublished data.
3. CURSCHMANN, L.: *Der Ileus und seine Behandlung*, Verhandl. d. deutsch. Kong. f. inn. Med., 1889, Wiesbaden.
4. FINE, J., BANKS, B. M., SEARS, J. B., and HERMANSON, L.: The treatment of gaseous distention of the intestine by the inhalation of 95 per cent oxygen, *Ann. Surg.*, 1936, ciii, 375.
5. FITZ, R. H.: The diagnosis and medical treatment of acute intestinal obstruction, *Trans. Congr. Am. Phys. and Surg.*, 1888, i, 1-42.
6. MILLER, C. J.: A study of 343 surgical cases of intestinal obstruction, *Ann. Surg.*, 1929, lxxxix, 91.
7. SENN, N.: The surgical treatment of intestinal obstruction, *Trans. Am. Coll. Surg.*, 1888, i, 43.
8. TREVES, F.: *Intestinal obstruction; its varieties with their pathology, diagnosis and treatment*, 1899, William Wood & Co., New York.
9. WANGENSTEEN, OWEN H.: The early diagnosis of acute intestinal obstruction with comments on pathology and treatment, with report of successful decompression of 3 cases of mechanical bowel obstruction by nasal catheter suction siphonage, *Trans. West. Surg. Assoc.*, 1931; also, *West. Jr. Surg.*, 1932, xl, 1-17.
10. WANGENSTEEN, OWEN H.: The therapeutic problem in bowel obstructions, 1937, Charles C. Thomas, Springfield, Illinois.
11. WANGENSTEEN, OWEN H., REA, CHARLES E., SMITH, BAXTER A., JR., and SCHWYZER, HANNS C.: Experiences with employment of suction in the treatment of acute intestinal obstruction: a reiteration of the indications, contraindications and limitations of the method, *Surg., Gynec. and Obst.*, 1939, lxviii, 5.
12. WANGENSTEEN, OWEN H., and REA, CHARLES E.: The distention factor in simple intestinal obstruction, *Surgery*, 1939, v, 327-339.

HISTOLOGIC STRUCTURE OF CARCINOMAS OF THE STOMACH AND QUALITY OF GASTRIC SECRETIONS *

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THE high incidence of hyposecretion of the stomach, hypochlorhydria and achlorhydria accompanying gastric cancer has long been known. The exact incidence varies in different statistics, and will also vary of course with the age of any group of patients since the frequency of achlorhydria unaccompanied by other apparent abnormalities increases with age.

In a group of 70 patients at the University of Chicago Clinics in whom carcinoma of the stomach was verified at operation or necropsy and who were for the most part in middle or advanced age, 38 (59 per cent) exhibited achlorhydria, 11 (16 per cent) exhibited hypochlorhydria and 21 (30 per cent) exhibited a normal type of gastric secretion. A little over half of the tests consisted of Ewald meals, in the remainder gastric secretion was tested by histamine. If histamine tests had been employed in every instance it is quite probable that the incidence of achlorhydrias in this series would have been reduced.

The cause of the high incidence of achlorhydria accompanying gastric cancer has been the subject of considerable speculation and a detailed review of this is beyond the scope of this report.¹ Suffice it to state that one of the most favored hypotheses at present is that it is due to gastritis, the result of or preceding the development of the cancer. This hypothesis, in the writer's opinion, meets with serious objection in that gastritis acute or chronic is by no means invariably associated with achlorhydria. And furthermore the moderate to severe gastritis observed in some instances of peptic ulcer is accompanied by at least normal degrees of acidity and frequently by hyperchlorhydria.

That the achlorhydria might be the result of the action upon the gastric mucosa of some factor elaborated by the tumor is a possibility that has been previously suggested but has received little serious consideration. If such a factor existed and since not all carcinomas are accompanied by achlorhydria it naturally follows that possibly some types of gastric carcinomas would be accompanied more often by achlorhydria or hypochlorhydria while other types would be relatively less often accompanied by such changes in secretion. A search of the literature has failed to reveal any attempts to correlate

* Received for publication December 10, 1938.

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This work was conducted as part of a study on the Effects of Extracts from Human Cancerous Stomachs on the Secretions of Gastric Juice in Dogs, supported by a grant from the International Cancer Research Foundation, Philadelphia, Pennsylvania.

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in significant numbers of cases, the quality of gastric secretion with the histologic types of the gastric cancer. The following report consists of such a study made in the series of cases mentioned above. To complete the observations note was also taken of the size and location of the lesions, although it has been amply shown by previous authors that these factors bear little relationship to the quality of secretion.

In the older literature it is stated that as carcinomas increase in size the character of gastric secretion becomes proportionately more altered toward reduction of volume and free acid. This would imply that in general there is little alteration at the inception of the growth. If the above were true there should be a definite relationship between size of lesion and character of gastric secretion. Of the 70 cases here studied reasonably accurate data as to size of the growth were available in 62 instances. The sizes were computed roughly in terms of square centimeters of surface of the lesions and these compared to the quality of secretion. The results are as follows:

(a) In 28 achlorhydric stomachs the average size of the lesion was 42 sq. cm.

(b) Of 8 stomachs exhibiting hypochlorhydria 2 were infiltrating growths involving the major portion of the stomach. And in the remaining 6, the average size of the lesion was 24 sq. cm.

(c) In 16 stomachs exhibiting a normal type of secretion the average size of the lesion was 21 sq. cm.

This might at first glance be taken to indicate a definite relationship between size of the tumor and achlorhydria. However, of the 28 achlorhydric stomachs 12 exhibited lesions varying in size from 6 to 24 sq. cm. with an average of 14.8 sq. cm. And in the group of 16 stomachs with normal types of secretion 5 exhibited lesions varying from 36 to 80 sq. cm. with an average of 49 sq. cm.

Location of the Neoplasm. In 52 cases the location of the lesion was compared with the character of gastric secretion. The results are tabulated as follows:

Type of Secretion	Location of the Neoplasm			
	Pyloric Region	Mid-Stomach	Cardiac Region	Entire Stomach Involved
Achlorhydria	24 cases	12 cases	2 cases	2 cases
Hypochlorhydria		4 cases	1 case	1 case
Normal type	5 cases	9 cases	1 case	

It would appear that no hard and fast relationship exists between the character of the secretion and the location of the tumor in this series. Of the 25 cases regarded as arising in the mid-stomach, half were accompanied

by a normal type of acid secretion or a hypochlorhydric juice. The higher incidence of achlorhydria observed in pyloric tumors might be explained on the assumption that in this group varying degrees of obstruction occurred more frequently than in cases in which the growths were located higher in the stomach and that such obstruction in the presence of carcinoma would in itself favor suppression of secretion and free acid.

Histologic Type of the Carcinoma. In 68 instances adequate material was available to permit of a histologic classification of the lesions. The sections were stained by hematoxylin and eosin. This classification was made as follows:

Adenocarcinoma. Marked tendency of the neoplastic cells to form tubules with lumina varying in size.

Medullary—predominant tendency of the cells to grow as solid masses with occasional tubular formation. This group includes the small cell types which are sometimes mistaken for round cell sarcoma.

Papillary—

Gelatinous—formation of mucinous-like substances within the growth. Typical colloid carcinomas are included in this group.

Scirrhus—infiltrating small cords of neoplastic cells with or without marked fibroplastic reaction about them and occasional tendency to form tubules.

The results are tabulated as follows:

	Achlorhydric Juices	Hypochlorhydric Juices	Normal Type of Secretions
1. Adenocarcinoma	15 cases	3 cases	5 cases
2. Medullary	8 cases	2 cases	6 cases
3. Papillary	6 cases	2 cases	
4. Gelatinous	6 cases	4 cases	4 cases
5. Scirrhus	0	1 case	5 cases

Among the first four groups there is no evidence to indicate a definite relationship between histologic type and quality of secretion. In the fifth group comprising six cases there were no instances of achlorhydria, in five the secretions were of normal character and one exhibited hyposecretion. The relatively small number of this group in the series coupled with the fact that in other instances no correlation was possible renders the data concerning it of very limited importance. The most that can be said is that in this series scirrhus carcinomas were not accompanied by achlorhydria whereas all the other types exhibited a high incidence of such secretion.

DISCUSSION

The several histologic types indicate several histogenetic histories in gastric cancer. Whether this also indicates several possible etiologies re-

lated to the various cell types is a question which of course cannot be answered. By inference, from the experimental work with carcinogenic hydrocarbons it would appear that varying histologic structure does not necessarily indicate varying etiology since the same hydrocarbon can be made to produce different histologic types of malignant neoplasms depending upon the normal tissues with which it is brought into contact (epidermoid carcinoma if applied to the skin, sarcoma if injected in the subcutaneous tissues).

That achlorhydria is observed in high incidence irrespective of cell type in gastric cancer would thus indicate that it is not the result of factors associated with the etiology of any specific histologic type.

In considering the question it should be borne in mind that a normal mechanism for inhibition of gastric secretion exists in the form of a "hormone" enterogastrone (Lim, Ivy²) in the mucosa of the upper small bowel, which is liberated by contact of this tissue with fat. That achlorhydria in cancer is the result of a stimulation of this mechanism under the conditions leading to or as a result of the formation of carcinoma in the stomach is a possible explanation for the occurrence of the phenomena. That it might also be the result of another substance formed prior to or accompanying gastric cancer, which exerts perhaps among other things an inhibitory effect upon secretion and free acid liberation is another possibility worthy of further study.

SUMMARY

In a series of 68 cases of carcinoma of the stomach representing several histologic types no correlation could be determined between the latter and the character of gastric secretion from such stomachs.

BIBLIOGRAPHY

1. POLLAND, W. S., and BLOOMFIELD, A. L.: Gastric secretion in cancer of the stomach, *Bull. Johns Hopkins Hosp.*, 1930, xlv, 307.
2. IVY, A. C., and GRAY, J. S.: Enterogastrone, *Cold Spring Harbor Symposia on Quantitative Biology*, 1937, v, 405.

TREATMENT OF PNEUMOCOCCIC PNEUMONIA; A COMPARATIVE STUDY OF 351 PATIENTS TREATED AT THE PHILADELPHIA GENERAL HOSPITAL *

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DURING the past few years a number of significant contributions to the therapy of pneumococcic pneumonia have been made. Cole¹ and his co-workers and others^{2, 3, 4} have demonstrated the efficacy of serum therapy. More recently, sulfapyridine⁵ has been found to be highly effective against the pneumococcus, and from early reports^{6, 7} it seems to be of unquestioned value in the treatment of pneumonia due to this organism. Both sero- and chemotherapy have gained many advocates, although there are still some⁸ who rely on non-specific remedies and claim equally good results. To evaluate the comparative merits of the various therapeutic agents now available it will be necessary to accumulate extensive data from different sources over a period of years. Of considerable value would be data collected in a single community or hospital where different methods of therapy were used. In this study we are presenting data from the Philadelphia General Hospital during the past pneumonia season (1938-1939) with the object of comparing the effectiveness of the several forms of treatment. In addition, the total mortality of the series can be compared to that of the past few years. The need for progress in the therapy of pneumonia is indicated by the high mortality rate of the disease among the patients admitted to a large city hospital. During 1936, 1937, and 1938 (January 1 to August 15) there were 535 typed adult pneumonia patients admitted to this hospital, with mortality rates of 35.2 per cent, 35.4 per cent, and 35.2 per cent respectively. The relatively small number of typed pneumococcic pneumonia patients reported during the past few years as compared to those in the present report is due to the more complete typing of the pneumococci with the further development and availability of specific anti-sera.

METHOD OF STUDY

Selection of Cases: The present study is based on 351 adult patients with typed pneumococcic pneumonia admitted to the Philadelphia General Hospital between August 15, 1938 and May 15, 1939. The diagnosis of pneumonia was established in each patient by the clinical history, and physical examination. In all patients included in this report a typed pneumococcus was recovered from the sputum or blood stream. Blood cultures were taken

* Received for publication August 11, 1939.

From the Wards of the Philadelphia General Hospital, Philadelphia, Pennsylvania, by courtesy of the Chiefs of the Medical Division.

in every instance, but some of these were not obtained until a few hours after treatment had been started. In the majority of patients the diagnosis was confirmed by roentgen-ray examination. The form of treatment used in each patient was left to the discretion of the chief of the service to which the patient was admitted. Specific serum, when indicated, was given routinely by several services, and, if serum was not available, sulfapyridine therapy or non-specific measures were employed. Sulfapyridine was used almost entirely on some of the services regardless of the type of pneumococcus and the duration of the disease. A number of patients fell into the non-specifically treated group because the pneumonia was in the process of resolution at the time of admission. None of these latter patients died. A small group received both serum and sulfapyridine. The non-specifically treated group received the usual supportive and symptomatic measures afforded any patient suffering with pneumonia, including oxygen therapy when it was indicated.

In those patients given serum there was considerable variation in the mode of administration and in the total amount of serum given because of the number of services involved. The serum was obtained, for the most part, from the Pennsylvania State Department of Health. Sulfapyridine* treatment was given according to the schedule described by our group⁷ in a previous communication.

COMPARATIVE THERAPEUTIC RESULTS

The comparative therapeutic results as obtained with non-specific treatment, with serum, and with sulfapyridine† are shown in table 1. The largest number of patients, 95, were in the Type I group. The mortality in the Type I cases was 3.3 per cent in the group to which sulfapyridine was administered and 11.1 per cent in the serum treated group. In the Type II group only 31 patients were observed. The non-specifically treated patients in this group represented those of advanced resolution on admission. There were 57 patients with Type III pneumonia, 16.2 per cent of the entire study. Serum was not available for these patients, and the mortality of 21.9 per cent obtained when sulfapyridine was used can be compared only with the 50 per cent mortality of the non-specifically treated group. The higher types of pneumonia were represented in scattered numbers and are too few to be of statistical significance.

Not included in table 1 are 14 patients who received both serum and sulfapyridine. In eight of these patients sulfapyridine was given only after apparent failure of serum-therapy. Although the disease was particularly severe in this group, only one patient died. The fatal case was a Type VII blood stream infection terminating fatally after two weeks of intensive

* The sulfapyridine was supplied to us through the courtesy of Merck and Company, Rahway, New Jersey.

† Most of the sulfapyridine treated patients are included in another report by our group (Am. Jr. Med. Sci.—in press).

TABLE I
Mortality and Incidence According to Pneumococcus Type

Type	Non-specific Treatment			Serum Treatment			Sulfapyridine Treatment		
	Number	Deaths	Mortality	Number	Deaths	Mortality	Number	Deaths	Mortality
			per cent			per cent			per cent
I	8	3	37.5	27	3	11.1	60	2	3.3
II	3	0	0.0	6	1	16.7	22	1	4.5
III	16	8	50.0	—	—	—	41	9	21.9
IV	4	1	25.0	1	0	0.0	14	1	7.2
V	5	1	20.0	2	0	0.0	26	1	3.8
VI	1	0	0.0	—	—	—	5	0	0.0
VII	4	0	0.0	4	0	0.0	11	1	9.1
VIII	6	0	0.0	6	0	0.0	11	1	9.1
IX	1	0	0.0	—	—	—	2	0	0.0
X	—	—	—	—	—	—	2	0	0.0
XI	1	0	0.0	1	1	100.0	—	—	—
XII	—	—	—	—	—	—	4	1	25.0
XIII	1	0	0.0	—	—	—	—	—	—
XIV	—	—	—	3	0	0.0	9	0	0.0
XV	1	0	0.0	—	—	—	4	1	25.0
XVI	—	—	—	—	—	—	3	1	33.3
XVII	—	—	—	—	—	—	1	0	0.0
XIX	—	—	—	—	—	—	5	1	20.0
XX	2	2	100.0	—	—	—	3	0	0.0
XXII	—	—	—	—	—	—	1	0	0.0
XXIII	—	—	—	—	—	—	2	0	0.0
XXIV	—	—	—	—	—	—	2	0	0.0
XXVII	—	—	—	—	—	—	3	0	0.0
XXVIII	—	—	—	—	—	—	1	1	100.0
XXIX	1	1	100.0	—	—	—	1	0	0.0
XXXI	1	1	100.0	—	—	—	—	—	—
TOTAL	54	17	31.5	50	5	10.0	233	21	9.0

therapy. Serum was given to five patients after failure of sulfapyridine to bring about the usual prompt therapeutic effect. None of these patients died. In addition, one patient with a Type IX blood stream infection, with a white blood count of 3300 (polys. 80 per cent) on admission, was given sulfapyridine. After 8 gm. had been administered, the drug was discontinued due to a progressive leukopenia (white blood cells 1500: polymorphonuclears 35 per cent). The patient then received serum (rabbit) with no apparent therapeutic effect and death followed within 24 hours.

In table 2 is shown the incidence of positive blood stream infections and their effect on mortality in the three therapeutic groups. The comparatively small number of patients with positive blood stream infections makes these data of questionable statistical significance. The relatively high mortality in patients with a bacteremia treated with sulfapyridine, and the lower mortality in patients treated with serum suggest that serum may have its greatest value in the management of patients with a positive blood culture.

The influence on the mortality of the day of the disease when treatment was begun is summarized for the three groups in table 3. As would be expected there was an increased mortality rate in the serum treated patients when therapy was delayed. This held true to a lesser extent in the sulfa-

TABLE II
Incidence of Bacteremia and Its Effect on Mortality Rate

Treatment	Blood Culture	Number	Total Deaths	Total Mortality
Non-specific	Positive	6	3	per cent
	Negative	48	14	50.0
	Total	54	17	29.2
Serum	Positive	8	0	0.0
	Negative	42	5	11.9
	Total	50	5	10.0
Sulfapyridine	Positive	25	5	20.0
	Negative	208	16	7.7
	Total	233	21	9.0

TABLE III
Influence of the Day of the Disease when Treatment was Begun

Day Treatment Began	Non-specific Treatment			Serum Treatment			Sulfapyridine Treatment		
	Number	Deaths	Mortality	Number	Deaths	Mortality	Number	Deaths	Mortality
			per cent			per cent			per cent
1	2	0	0.0	4	0	0.0	18	1	5.5
2	7	1	14.3	19	1	5.3	32	1	3.1
3	5	4	80.0	9	1	11.1	34	0	0.0
4	9	6	66.7	12	2	16.7	45	3	6.7
5	8	3	37.5	6	1	16.7	39	5	12.8
6	8	0	0.0	—	—	—	23	4	17.4
7	6	1	16.7	—	—	—	18	3	16.7
8	3	2	66.7	—	—	—	7	0	0.0
9	2	0	0.0	—	—	—	3	1	33.3
9+	4	0	0.0	—	—	—	14	3	21.4

pyridine treated group. The highest death rate took place in the advanced age groups as shown in table 4. The fatal cases are briefly presented in tables 5 and 6.

TABLE IV
Influence of Age Groups on Mortality

Age Group	Non-specific Treatment			Serum Treatment			Sulfapyridine Treatment		
	Number	Deaths	Mortality	Number	Deaths	Mortality	Number	Deaths	Mortality
			per cent			per cent			per cent
years									
12-19	7	1	14.3	8	—	0.0	22	—	0.0
20-29	11	2	18.2	13	1	7.7	44	1	2.3
30-39	6	1	16.7	16	2	12.5	48	3	6.3
40-49	9	2	22.2	6	1	16.7	58	6	10.4
50-59	11	6	54.5	5	1	20.0	33	4	12.1
60-69	6	4	66.7	1	0	0.0	20	3	15.0
70 and over	4	1	25.0	1	0	0.0	8	4	50.0

TABLE V
Analysis of Fatal Serum-Treated Cases

Number	Age	Day of Disease Treatment Began	Type	Total Dosage	Remarks
	years			units	
1	29	3	1	300,000	None
2	58	5	1	200,000	Jaundice
3	45	4	2	160,000	Acutely ill on admission
4	39	4	1	60,000	Hypertensive
5	35	2	11	160,000 (rabbit)	Alcoholic

Analysis of Non-specific-Treated Cases

1	17	5	1		None
2	33	3	1		Bacteremia
3	54	8	1		Moribund on admission
4	56	8	3		None
5	58	4	3		None
6	48	5	3		None
7	60	4	3		Bacteremia
8	54	5	3		Cardiac failure
9	21	4	5		Thyrotoxicosis
10	45	4	20		Bacteremia
11	50	3	29		None
12	50	3	29		None
13	71	7	3		None
14	60	2	31		Moribund on admission
15	29	3	20		Cardiac decompensation
16	65	4	4		Developed empyema
17	69	3	3		Heart disease

INFLUENCE OF THERAPY ON THE COURSE OF THE DISEASE

In comparing various methods of therapy, we have attempted to evaluate their influence on the course of the disease as well as their influence on the death rate. The most striking observation in the serum and sulfapyridine treated patients was the frequency with which the institution of treatment was followed within 24 to 48 hours by a critical drop in temperature (see table 7). This was particularly true in those receiving sulfapyridine. In the non-specifically treated group the prompt fall in temperature was, in many instances, associated with advanced resolution at the time of admission to the hospital. No significant differences could be detected by physical or roentgen-ray examinations in the rate of resolution in the three therapeutic groups. In the serum and sulfapyridine treated patients the early drop in temperature was usually followed by definite clinical improvement which was not necessarily accompanied at once by any appreciable change in the lung signs.

TABLE VI
Analysis of Fatal Sulfapyridine-Treated Cases

Number	Age	Day of Disease Treatment Began	Type	Total Dosage	Remarks
	years			gm.	
1	44	6	1	8	Moribund on admission
2	73	1	2	24	None
3	47	8+	3	20	Bacterial endocarditis
4	79	5	3	25	Cardiac failure
5	58	7+	3	25	Chronic alcoholism
6	45	9	3	19	Bacteremia
7	90	4	3	3	Moribund on admission
8	62	5	4	11	Moribund on admission. Bacteremia
9	32	6	7	35	Meningitis. Empyema. Bacteremia
10	40	14+	8	4	Moribund on admission
11	56	5	15	25	Cardiac failure
12	37	7+	16	5	Paresis. Moribund when treatment started. Bacteremia
13	37	7	28	25	Temperature normal, lungs clear, severe diabetes, insulin shock
14	40	4	12	8	Alcoholic. Uremic
15	63	6	3	25	Cardiac failure
16	52	4	1	16	Moribund on admission. Diabetic
17	29	6	19	8	Chronic alcoholism
18	78	5	5	4	Moribund on admission
19	52	5	3	25	Cardiac failure. Recovered from pneumonia. Bacteremia
20	47	14	3	9	Moribund on admission. Cardiac failure
21	66	2	3	35	Cardiac failure

TABLE VII

Day of Fall in Temperature	Type of Treatment		
	Non-specific	Serum	Sulfapyridine
	per cent	per cent	per cent
1	21.6	8.9	61.2
2	27.3	40.0	20.8
3	2.7	17.8	5.6
4	24.3	22.2	4.2
4+	24.3	11.1	8.0

COMPLICATIONS

Empyema proved the most frequent complication, occurring once in the non-specifically treated group and in five patients in each of the serum and sulfapyridine treated groups, an incidence of 10 per cent, in those receiving serum and 2.3 per cent in the sulfapyridine group. The low incidence of empyema in the non-specifically treated group may be due to the fact that the number of Type I infections in this group is comparatively small. Massive pleural effusions were observed in 6 patients, one in the serum treated

group and five in the drug treated group. Delayed resolution was detected in four sulfapyridine treated patients. Meningitis occurred in one instance in this same group. It is our belief that abdominal distention was less in the serum and sulfapyridine treated patients than in the non-specifically treated group.

TOXIC REACTIONS

In the serum treated patients there was one instance of an immediate serum reaction and four patients developed delayed serum sickness. The most common untoward effects in the sulfapyridine treated group were nausea and vomiting. Nausea occurred in approximately 85 per cent of the patients, being most severe during the first 24 hours of drug treatment. Vomiting was seen in 52 per cent of the patients, but was severe in only six instances. In none was the vomiting severe enough to necessitate the discontinuance of sulfapyridine before a satisfactory therapeutic effect had been obtained. Drug fever occurred in 11 patients, mild hallucinatory psychoses developed in four, and two showed progressive leukopenia. The red count and hemoglobin likewise fell in a number of cases, but in view of the marked dehydration of most of the patients on admission it was difficult to evaluate this apparent secondary anemia. This drop in the red count and hemoglobin was observed in all three therapeutic groups but more so in the sulfapyridine treated patients. No cases of acute hemolytic anemia were observed. In addition, there were 11 instances of microscopic hematuria and one with gross hematuria following the administration of sulfapyridine. Azotemia without hematuria developed in one patient after receiving the drug, but after therapy was stopped the blood urea nitrogen returned to normal. The drug was given for the second time and the elevated blood urea nitrogen re-occurred, dropping again with a cessation of sulfapyridine.

COMMENT

We realize that enough data have not been accumulated as yet to evaluate adequately the comparative merits of the various forms of treatment. We believe that serum and sulfapyridine have aided materially in the reduction of the mortality rate of pneumococcic pneumonia at the Philadelphia General Hospital from approximately 35 per cent for the past few years, to 12.5 per cent for the cases considered in this report. In this hospital serum has been used for the past few years but in only a comparatively small percentage of patients.

Whether the low mortality figure of the past pneumonia season indicates a reduction in the severity of the disease cannot be ascertained at this time. While a variation in the virulence of the pneumococcus is possible, this variation is less apt to occur in the lower types, particularly in Type I infections. In this paper we have presented 95 cases of Type I pneumonia with mortality rates of 37.5 per cent, 11.1 per cent, and 3.3 per cent in the non-specific,

serum, and sulfapyridine treated groups respectively. The only definite conclusion which we may draw from these figures is that serum therapy and sulfapyridine therapy both represent significant advances in the treatment of pneumococcal pneumonia. Whether the combination of serum and sulfapyridine will prove more effective than either alone cannot be ascertained until more data are collected.

SUMMARY

1. A comparative study of the efficacy of various forms of treatment in 351 adult pneumococcal pneumonia patients treated at the Philadelphia General Hospital between August 15, 1938 and May 15, 1939 is presented.

2. Mortality rates of 31.5 per cent, 10.0 per cent, and 9.0 per cent were obtained with non-specific, serum, and sulfapyridine treatment respectively.

3. The total mortality rate of this series, 12.5 per cent, is compared to that of approximately 35.0 per cent for the past few years.

REFERENCES

1. COLE, R.: The treatment of pneumonia, *Ann. Int. Med.*, 1936, x, 1-12.
2. CECIL, R. L., BULLOWA, J. A., CHICKERING, H. T., and CORWIN, E. H.: Community provision for the serum treatment of pneumococcal pneumonia, *Jr. Am. Med. Assoc.*, 1937, cix, 1323-1328.
3. BLANKENHORN, M. A.: Present status of serum therapy of lobar pneumonia, *Jr. Am. Med. Assoc.*, 1938, cxi, 1260.
4. BULLOWA, J. G. M.: Management of the pneumonias, 1937, Oxford University Press, New York.
5. WHITBY, L. E. H.: Chemotherapy of pneumococcal and other infections with 2-(p-aminobenzenesulfonamido) pyridine, *Lancet*, 1938, i, 1210.
6. EVANS, G. M., and GAISFORD, W. F.: Treatment of pneumonia with 2-(p-aminobenzene-sulfonamido) pyridine, *Lancet*, 1938, ii, 14.
7. FLIPPIN, H. F., LOCKWOOD, J. S., PEPPER, D. S., and SCHWARTZ, L.: The treatment of pneumococcal pneumonia with sulfapyridine, *Jr. Am. Med. Assoc.*, 1939, cxii, 529-534.
8. Correspondence, Pneumonia in private practice, *Jr. Am. Med. Assoc.*, 1939, cxii, 168-169.

PICROTOXIN IN THE TREATMENT OF ACUTE BARBITURATE POISONING; A REVIEW OF THE LITERATURE WITH REPORT OF TWO CASES*

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ACUTE poisoning with barbituric acid compounds ranks today as one of the commonest forms of acute drug intoxication; therefore, it has become a necessity for physicians to be familiar with the most satisfactory methods of treating this condition. A review of the recent clinical reports in the literature seems to indicate that picrotoxin, properly employed, is at present the most successful antidote for barbiturate poisoning. Table 1 summarizes the data of the cases in these reports. To them we are adding the two cases herein recorded, one of which is of unusual interest because the patient recovered after the ingestion of what we believe is the largest dose of barbital as yet reported in a picrotoxin-treated case.

CASE REPORT

Case 1. S. T. N., a woman, aged 39, white, weighing 142 pounds (64.5 kg.), after being despondent for several weeks, swallowed with suicidal intent 49 five grain tablets of barbital, a total dose of 245 grains (16.3 gm.). She was found in deep coma about 14 hours later. Dr. J. W. M., who was called, brought her at once to St. Joseph's Hospital, Syracuse. Apparently no vomiting had occurred, so it may be assumed that the entire dose was retained.

When first seen by Dr. E. C. R., Sr., in consultation, the patient was unconscious, with constricted pupils, insensitive corneae, and absent reflexes. The heart sounds were of good quality; the lungs without moisture. Respiration was regular but shallow with a rate of 40 per minute; the pulse was 104 beats per minute and the rectal temperature 96.8° F. The blood pressure was 80 mm. of mercury systolic and 70 mm. diastolic. A bleb the size of a quarter was present over the outer surface of each ankle. The patient received immediately a gastric lavage with sodium bicarbonate solution from which clear returns were obtained. An attempt was made to secure picrotoxin, but none could be found in any of the local hospitals. During the interim she was given caffeine sodium benzoate 0.5 gm. intramuscularly every hour; coramine 1.5 c.c. intramuscularly every one half hour for six doses and then every hour; oxygen and carbon dioxide continuously by tent; and an intravenous infusion of 1000 c.c. of 5 per cent dextrose and 1000 c.c. of normal saline. A retention catheter was inserted.

Nine hours after admission and 23 hours after ingestion, the condition of the patient had failed to improve in spite of treatment, and a fatal outcome seemed certain. Moist bubbling râles were present in the chest and the respiration was noisy.

* Received for publication November 9, 1938.

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TABLE I
Cases of Acute Poisoning with Barbiturate Compounds Treated with Picrotoxin
(Compiled from the literature)

Author	Case	Sex	Age	Barbituric Acid Compound Causing Poisoning and Amount Taken (gm.)		Hours Before Treatment Instituted	Picrotoxin		Other Treatment	Complications	Outcome
							Total Amount (mg.)	Usual Dosage Employed			
Arnett ² May 20, 1933	1	f	3 $\frac{3}{4}$	Amytal	0.4	3 plus	1.3	2 doses 1/100 grain each by vein	Ipecac, gastric lavage and ephedrine	None	Recovered
	A	f	68	Phenobarbital	5 plus	36	167	10 mg. every $\frac{1}{2}$ hour by vein	None	Broncho-pneumonia, lung abscess	Talking, eating, but died 103 hr. after admission
Volpito ⁴ April 8, 1937 (c.f. Rovenstine ⁵ cases 1 and 2)	B	m	68	Amytal	3.9	3	24	3 mg. every 3 hours 9 mg. by muscle 15 mg. by vein	None	None	Recovered
	1	f	33	?	?	1 to 36 ?	18	2 doses 9 mg. (by vein?) at 20 minute interval	Epinephrine, caffeine, ephedrine, metrazol, infusions 50% dextrose, infusions 5% dextrose in normal saline, digitalis, strychnine, clyses 5% dextrose and normal saline	Circulatory failure, and pulmonary edema	Not aroused, died 45 hours after admission
Burstein and Rovenstine ⁵ May 1937	1	f	young	Sodium amytal	7.8	30	157	By vein with infusion during 6 hours	Gastric lavage, strychnine, infusions 5% dextrose; artificial respiration	None	Recovered
	1	f	32	Phenobarbital amytal	⁴ 1.2	11	131	By vein slowly during 48 hrs.	Supportive measures, strychnine	None	Recovered

TABLE I (Continued)

Author	Case	Sex	Age	Barbituric Acid Compound Causing Poisoning and Amount Taken (gm.)	Hours Before Treatment Instituted	Picrotoxin		Other Treatment	Complications	Outcome
						Total Amount (mg.)	Usual Dosage Employed			
Kline, Bigg and Whitney ⁷ July 31, 1937	1	m	20	Amytal 3	3	69	23 subcutaneous injections of 3 mg. in 16 hours	Strychnine, gastric lavage, infusions 5% dextrose	Bronchopneumonia	Recovered
	2	m	young	Sodium amytal 8	8 to 10	2	3 doses 1/100 grain each (by vein?) during 4 hours	Coramine, gastric lavage, magnesium sulfate, benzedrine, infusions dextrose and normal saline, strychnine, oxygen and carbon dioxide	None	Recovered
Rovenstine ⁹ July 1938 (c.f. Volpitta ⁴ who previously reported cases 1 and 2)	1	f	24	Sodium amytal 7.6	12	129	3 mg. by vein irregularly during 9 hours	Strychnine, coramine, gastric lavage, endotracheal airway, suction, caffeine, infusion 5% dextrose in normal saline all without effect until picrotoxin was given	Pulmonary edema, and bilateral ulnar palsy	Recovered
	2	f	28	Sodium pentobarbital 6	8	48	By vein in 1 hr.	Gastric lavage, infusion 5% dextrose in normal saline, airway	None	Recovered
	3	f	45	Phenobarbital 5	12	122	By vein 15 mg., 30 mg. and 8 mg. during 8 hours; later 3 mg. by muscle every 10 to 30 minutes	Caffeine, coramine, gastric lavage, calomel, mercupurin, infusion 5% dextrose in normal saline, oxygen	None	Recovered

TABLE I (Continued)

Author	Case	Sex	Age	Barbituric Acid Compound Causing Poisoning and Amount Taken (gm.)		Hours Before Treatment Instituted	Picrotoxin		Other Treatment	Complications	Outcome
							Total Amount (mg.)	Usual Dosage Employed			
Kohn, Platt and Saltman, ¹⁰ July 30, 1938	4	m	57	Sodium barbital	33.3	7 to 8	2134	By vein infusion 1 mg. per minute; by muscle about 20 mg. per hour for 20 hours	Strychnine, frequent gastric lavage, lumbar puncture, infusions 5% dextrose in normal saline, mercupurin	Acute hepatitis, hypostatic pneumonia	Talked 3rd day, then relapsed; died 8th day after admission
	1	f	36	Phenobarbital	?	20	671	Small doses by vein and muscle frequently during 4 days	Caffeine, coramine, strychnine, atropine, and infusions of 10% dextrose in saline without effect; then prompt response to picrotoxin. Later given strophanthin, 50% dextrose and oxygen and carbon dioxide for edema of lungs	Pulmonary edema	Recovered
	2	f	63	Barbital	?	12	60	6 to 12 mg. by vein during 2 hours	Infusions of dextrose, digitalis	Circulatory failure; pulmonary edema	Never aroused; died 4 hrs. after admission
	3	f	23	Sodium pentobarbital	?	Several	21	3 doses of 6, 12, and 3 mg. during 1 hour (by vein?)	Infusion 50% dextrose, ephedrine, strychnine, and coramine without effect; then prompt response to picrotoxin	None	Recovered
	4	m	30	Barbital Sodium pentobarbital	6.5 0.6	8 plus	228	3 to 9 mg. by vein every 10 to 20 minutes; later every 2 hrs. by muscle	Gastric lavage, rectal drip, caffeine, strychnine, infusions 25% dextrose, and clyses	None	Recovered

TABLE I (Continued)

Author	Case	Sex	Age	Barbituric Acid Compound Causing Poisoning and Amount Taken (gm.)	Hours Before Treatment Instituted	Picrotoxin		Other Treatment	Complications	Outcome
						Total Amount (mg.)	Usual Dosage Employed			
Bleckwenn and Masten ¹¹ Aug. 6, 1938	1	f	63	Sodium amytal 0.2	9 plus	24	Single dose 15 mg. by vein followed in 15 minutes by 9 mg.	Caffeine	None	Recovered
	2	f	21	Sodium amytal Sodium pentobarbital 1.16	?	669	Frequent doses by vein during 10 hours	Caffeine, coramine, infusions of sucrose, parenteral fluids	Anoxia, edema and medullary death	Never aroused; died 79½ hrs. after admission
	3	m	54	Sodium amytal 7.6	8 plus	68	Small doses by vein during 3 hours	None	None	Recovered
	4	f	23	Sodium amytal 10	24	148	Small doses by vein during 3 hours	Oxygen, clyses, metrazol, caffeine, infusions of sucrose and dextrose	None	Recovered
	5	f	30	Sodium amytal Phenobarbital 5.2 0.4	1½	60	Small doses by vein during 3 hours	Gastric lavage, caffeine	Lobar pneumonia, cystitis	Recovered
	6	f	24	Sodium amytal 8	Few	30	Single dose 10 hours after admission (by vein?)	Gastric lavage with potassium permanganate, oxygen, airway, coramine, epinephrine, infusions 10% dextrose, 5% dextrose, and Ringer's solution	None	Recovered

TABLE I (Concluded)

Author	Case	Sex	Age	Barbituric Acid Compound Causing Poisoning and Amount Taken (gm.)	Hours Before Treatment Instituted	Picrotoxin		Other Treatment	Complica-tions	Outcome
						Total Amount (mg.)	Usual Dosage Employed			
Reifenstein, et al.	1	f	39	Barbital	14	314	Starting 9 hrs. after admission 216 mg. by vein during 4 hours 6 hrs. later 20 mg. by vein during 4 hours 1 hr. later 60 mg. by vein during 8 hours Then 3 mg. by muscle every 3 hrs. for 6 doses	Gastric lavage, caffeine, coramine, oxygen and carbon dioxide, infusions 5% dextrose and normal saline, all without effect. Prompt response to picrotoxin which was alternated with 50% sucrose. Additional infusions 5% dextrose and normal saline. Caffeine and coramine continued	Pulmonary congestion; cystitis; pharyngeal irritation	Recovered
	2	m	49	Seconal	8 to 10	24	1 : 2000 solution, 50 c.c. by vein, given 2 c.c. per minute	Infusion 5% dextrose and normal saline given with picrotoxin. Later infusion sucrose, followed by 5% dextrose and normal saline	Severe convulsion	Recovered

Mucus was aspirated from the throat at frequent intervals. At this time a supply of picrotoxin* was located, and, under the supervision of Drs. E. C. R., Sr., E. C. R., Jr., and J. W. M., during the next few hours an infusion of 250 c.c. of 5 per cent dextrose containing 216 mg. of picrotoxin was given by vein slowly and intermittently. This was alternated with an infusion of 500 c.c. of 50 per cent sucrose intravenously which produced marked diuresis. About one hour after the picrotoxin was begun the patient reacted for the first time to painful stimuli; six hours later she began to groan occasionally. Ten hours after picrotoxin was first administered, an intravenous infusion of 2000 c.c. of 5 per cent dextrose containing 20 mg. of picrotoxin was begun and allowed to run in slowly during a period of four hours. This was followed by an infusion of 500 c.c. of 50 per cent sucrose which produced diuresis as before. The caffeine and the coramine were continued. While this treatment was being given the patient began to move her head from side to side, and to raise her arms.

Forty-seven hours after ingestion of the barbital and 24 hours after the picrotoxin therapy was instituted the patient was considerably improved. The moisture had disappeared from the chest; the pulse was of better quality and its rate 112 beats per minute; the respirations were 36 per minute; and the blood pressure had risen to 118 mm. of mercury systolic and 60 mm. diastolic. During the next eight hours 60 mg. of picrotoxin in an infusion of 1000 c.c. of 5 per cent dextrose were administered slowly and intermittently by vein. This was again followed by an intravenous infusion of 500 c.c. of 50 per cent sucrose. Impacted feces were removed by a retention enema and a colonic irrigation. The patient became increasingly more restless, moved her head and shoulders, and opened her eyes, but was not fully conscious.

Fifty-nine hours after ingestion the patient would open her eyes when called. From then on picrotoxin 3 mg. was given intramuscularly every three hours. The coramine and the caffeine were continued. An intravenous infusion of 500 c.c. of 50 per cent sucrose was administered, followed later by an intravenous infusion of 1000 c.c. of 5 per cent dextrose and 500 c.c. of normal saline. About 73 hours after ingestion the patient became conscious, asked for her husband, and took sips of water. At that time the picrotoxin was discontinued, six doses (18 mg.) having been given intramuscularly. This made a total of 314 mg. of picrotoxin administered. During the administration of picrotoxin the patient was constantly under the personal supervision of one or more of us (Drs. E. C. R., Jr., E. C. R., Sr., J. W. M., and A. J. R.).

Five hours later the patient had a severe chill with a temperature rectally of 104° F., following an intravenous infusion of 500 c.c. of 50 per cent sucrose. A few râles were detected in the right mid-lung field. A roentgen-ray film of the chest taken shortly after was interpreted by Dr. Donald S. Childs as showing increased pulmonary markings. Within 24 hours, however, the râles had disappeared and the temperature had returned to normal. The patient was given as much fluids by mouth as she would take. Thereafter her convalescence was uneventful except for a mild cystitis and a moderate irritation of the pharynx, both of which responded readily to treatment. All of the reflexes returned, and the patient had no residual paralyses. Several blebs present on the ankles on admission healed slowly. She was discharged completely recovered 10 days after admission.

During each of the first four days the intake of the patient was two to three liters of fluid by vein, and the output was approximately two liters. Very satisfactory diuresis was obtained after each infusion of sucrose. The urine on several occasions

* Picrotoxin employed in Case 1 was in part furnished through the courtesy of Abbott Laboratories, North Chicago. The remainder, purchased in the open market, was packaged as a veterinary preparation (Abbott) but was utilized for man as it was the only picrotoxin available.

Picrotoxin employed in Case 2 was furnished through the courtesy of Eli Lilly and Company, Indianapolis.

showed numerous red blood cells and a one plus albumin, but these findings disappeared before discharge. Quantitative determinations of the amount of barbitol in the urine¹ could not be satisfactorily completed because of incontinence, but several specimens revealed 0.25 to 0.5 mg. of barbitol per c.c. of urine. No evidence of jaundice was detected at any time. The patient on returning to consciousness admitted her suicidal attempt and verified the nature and the amount of the drug taken.

SUMMARY OF CASE 1

A woman of 142 pounds (64.5 kg.) body weight survived a total dose of 16.3 gm. (245 grains) of barbitol, taken with suicidal intent. The patient remained untreated for about 14 hours and was found in deep coma; she failed to respond to physical stimulation, gastric lavage, caffeine, coramine, oxygen and carbon dioxide, and intravenous infusions of dextrose and saline for nine additional hours. Improvement began within one hour after picrotoxin was first administered intravenously, and the patient became conscious and rational about 73 hours after ingestion, at which time a total of 314 mg. of picrotoxin had been given. Aspiration of mucus by suction, and diuresis induced by concentrated sucrose by vein aided materially in the favorable response. The patient developed transitory pulmonary congestion, mild cystitis and pharyngeal irritation which did not interfere with convalescence. She was discharged completely recovered 10 days after admission.

Case 2. C. D. N., a man, aged 49, white, weighing 180 pounds (81.8 kg.), after several weeks of depression, swallowed with suicidal intent between five and ten 1½ grain tablets of seconal, a total dose of 7½ to 15 grains (0.5 to 1 gm.). He was found in coma eight to 10 hours later. Dr. George C. Goewey,* who was called, had the patient transferred at once to the Syracuse Memorial Hospital. There was no evidence of vomiting, and it may be assumed that the entire dose was retained.

When first seen by Dr. E. C. R., Jr., in consultation, the patient was unconscious, with moderately constricted pupils, good color, and normal reflexes. With vigorous physical stimulation he would move arms and legs, turn his head and open his eyes, but would not respond when called and appeared unconscious. The heart sounds were of good quality; the lungs without râles. Respiration was regular and shallow with a rate of 20 per minute; the pulse was 88 beats per minute; and the rectal temperature 98.2° F. The blood pressure was 130 mm. of mercury systolic and 70 mm. diastolic. No blebs were present on the skin, and no cyanosis was apparent. Although the dosage of medication was then unknown, it appeared reasonably certain that the patient had not ingested a fatal amount of the barbiturate, and that he would recover without treatment. At the same time it was felt advisable to institute the following therapy.

Picrotoxin 24 mg. was added to 50 c.c. of normal saline containing 5 per cent dextrose, and the mixture given intravenously at the rate of 2 c.c. per minute. Within 10 minutes the respirations became deeper and the patient began to move spontaneously; five minutes later he appeared to understand what was said and responded to questions by moving his head. The picrotoxin infusion was completed in 25 minutes and immediately 200 c.c. of 50 per cent sucrose were given by vein. The patient became progressively more alert, and began to talk. He admitted his suicidal attempt, identified the barbiturate taken, and estimated that he had ingested between five and 10 tablets.

One and one-half hours after the picrotoxin was first administered the patient had a violent convulsion lasting 20 minutes, during which time he developed stertorous breathing with frothy sputum, became extremely cyanotic, and exhibited twitching of the individual muscles of the face and arms and occasional gross spasms involving

* We are indebted to Dr. George C. Goewey for the privilege of treating and reporting case 2.

all of the limbs. He became semicomatose and unresponsive. For over one-half hour after the major seizure had ceased the patient continued in this condition with gradually decreasing twitching of the muscles. During this period 1000 c.c. of 5 per cent dextrose in normal saline were administered by vein. Shortly after, he awakened and rapidly became clear mentally. Three hours after the picrotoxin had been given he swallowed a glass of water which he vomited in a few minutes. Within another hour, however, he was able to retain fluids given by mouth. During this entire period there had been no significant changes in the pulse or the blood pressure. Thereafter the patient made an uneventful recovery and was discharged two days after admission.

A urine specimen obtained by catheter shortly after the patient was admitted revealed a trace of albumin and numerous pus cells and hyaline casts. Tests for the presence of barbital in the urine¹ were negative.

SUMMARY OF CASE 2

A man of 180 pounds (81.8 kg.) body weight survived an estimated total dose of 0.5 to 1 gm. (7½ to 15 grains) of seconal, taken with suicidal intent. The patient remained untreated for eight to 10 hours and was found in a semicomatose condition, but within one hour after the intravenous administration of 24 mg. of picrotoxin was first begun he was conscious and rational. One-half hour later the patient had a severe convulsion lasting 20 minutes, followed by muscular twitching. Thereafter his convalescence was uneventful and he was discharged completely recovered two days after admission.

COMMENT

The difficulty in estimating the fatal dose of barbituric acid derivatives is well recognized. Among the factors to be considered are the marked individual susceptibility to the action of the drug, the weight and the age of the victim, the nature of the stomach contents, the presence or absence of emesis at the early state of absorption, the amount and the rate of absorption, the duration of time before the treatment is instituted, the presence of complicating conditions such as pneumonia or circulatory failure, and the methods by which the antidotal, evacuant and supportive measures are employed, as well as the nature of the antidotes themselves.

Weiss,¹² from a careful review of the literature, has concluded that the fatal dose of barbital usually varies between 10 to 15 gm. (150 to 225 grains), but that death may result from much smaller doses, and larger doses may be followed by recovery. Fantus¹³ states that the nearly always fatal dose of barbital is about 10 gm. (150 grains). He reports that the mortality rate may exceed 20 per cent. Purves-Stewart and Willcox¹⁴ place the average minimum fatal dose of barbital at 3.25 gm. (50 grains). On the other hand they state that patients receiving quantities as large as 13 gm. (200 grains) and even more have been known to recover under suitable treatment. Weiss¹² considers the fatal dose of phenobarbital to vary between 4 to 6 gm. (60 to 90 grains); Fantus¹³ places it at 4 gm. (60 grains). Sollmann¹⁵ states that 2 to 3 gm. (30 to 45 grains) of amytal is usually fatal to man. The dose of pentobarbital which is generally fatal is given by Koppanyi¹⁶ as 1 gm. (15 grains). Seconal has been so recently introduced

that the usually fatal dose is at present unknown. The sodium salts of the barbituric acid derivatives in man appear to have approximately the same lethal qualities as the uncombined compounds.

In table 1 is presented a review of 24 cases of acute barbiturism treated with picrotoxin. The type of barbituric acid derivative was unknown in one case; more than one barbital compound was ingested in four other cases. Of the remainder, 10 patients took amytal; three barbital; three phenobarbital; two pentobarbital; and one seconal. Five of the 24 cases died. Of the 20 cases that recovered, two had ingested unknown quantities of drug; four amounts less than the usually fatal dose; and 14, amounts in excess of the usually fatal dose. Of the cases that died, the amount ingested was unknown in two and was more than the usually fatal dose in the other three. The causes of death were given as: (1) bronchopneumonia and lung abscess; (2) circulatory failure and pulmonary congestion; (3) acute hepatitis and hypostatic pneumonia; (4) circulatory failure and pulmonary edema; and (5) medullary anoxia and edema. Among the recovered cases there were two cases with pneumonia, three with pulmonary congestion, two with cystitis, one with bilateral ulnar nerve palsy, and one with pharyngeal irritation. The increased gravity of the prognosis in the presence of pulmonary and circulatory complications is apparent. Outstanding in the data on picrotoxin administration is the use of frequently repeated small doses intravenously and the relatively prompt response of the patient after institution of this therapy. The necessity for persistent and prolonged treatment is clearly demonstrated.

We have not succeeded in finding the report of any patient other than our own case 1 who recovered from more than the fatal dose of barbital after the use of picrotoxin. A number of spectacular recoveries after other therapeutic measures are reported, however. Purves-Stewart and Willcox¹⁷ recorded the case of a young woman who ingested a mixture of barbital, allonal, quadroux, and ipral totaling 31 gm. (475 grains) and recovered, in spite of the fact that she was untreated for 14 hours and developed a complicating pneumonia. She received gastric lavage, dextrose, coffee by rectum, caffeine, coramine, atropine, strychnine, and repeated cisternal punctures. Chang and Tainter¹⁸ reported recovery from 18 gm. (270 grains) of barbital sodium with treatment consisting only of supportive fluids, caffeine and camphor in oil. Mme. Bertrand-Fontaine and Claass¹⁹ recorded the recovery of a girl who was untreated for 10 hours after ingesting 17 gm. (255 grains) of barbital. She received 390 mg. of strychnine by vein in small doses every one to three hours for 64 hours. Weiss¹² mentions a case that recovered from 17 gm. (255 grains) of barbital. He does not mention the therapy employed.

On the basis of analogy with these cases, the recovery of Case 1 could not rightfully be attributed to the picrotoxin. But the prompt response of the patient after other methods of stimulation had failed was impressive.

A careful study of the cases of table 1 reveals many similar situations in which picrotoxin proved life saving when other measures were without effect.

As has been stated, Case 2 probably would have recovered without any treatment, but again the response to picrotoxin was prompt and dramatic. The uncertainty as to the exact dosage of seconal ingested is occasioned by the fact that the tablets were taken intermittently and during the intervening time the patient became so drowsy (because of the rapid action of seconal) that he was unable to recall the exact number swallowed. Confirmation of the dosage is obtained from the relatively small amount of picrotoxin required to produce recovery. Indeed, it seems that an excess of picrotoxin was administered which produced the alarming convulsion. It is possible that the toxicity of the picrotoxin was enhanced by the dehydrating action of the sucrose, a synergism advantageous in the presence of an excess of barbiturate, but dangerous to the patient in the absence of barbiturate to be counteracted. In this case a more dilute solution of picrotoxin more slowly administered would have been a safer therapeutic procedure.

The following treatment program which we have evolved follows in general that suggested by Bleckwenn and Masten¹¹: (*a*) gastric lavage and purgation with sodium phosphate; (*b*) continuous oxygen by tent; (*c*) frequent aspiration of mucus, with endotracheal intubation if needed; (*d*) picrotoxin intravenously; (*e*) sucrose intravenously for diuresis and dehydration of brain and lung; (*f*) dextrose and saline intravenously to supply fluids, to furnish energy, and to prevent acidosis; (*g*) indwelling catheter in urethra; (*h*) lumbar puncture to relieve increased intracranial pressure when present; (*i*) external heat; (*j*) oil retention enema and colonic irrigation to avoid fecal impaction; and (*k*) blood transfusion to combat severe anemia.

RÉSUMÉ

1. A case of acute barbiturism from the ingestion of 16.3 gm. (245 grains) of barbital, with recovery after the use of 314 mg. of picrotoxin, is reported. A second case with recovery from 0.5 to 1 gm. (7½ to 15 grains) of seconal after the use of 24 mg. of picrotoxin is presented.

2. Twenty-two additional cases of acute barbiturate intoxication treated by picrotoxin are collected from the literature. Of these, five died, two recovered from unknown quantities of medication, three recovered from small quantities, and 12 recovered from doses of more than the usually fatal amount.

3. These cases furnish striking evidence that picrotoxin is effective in acute barbiturism, frequently when other measures have failed.

4. A program for treating acute poisoning with barbituric acid compounds is outlined.

SUPPLEMENTARY REPORT *

Since this paper was submitted for publication in November 1938, there have appeared a number of communications dealing with the use of picrotoxin in barbiturate poisoning.

In February 1939 the Council on Pharmacy and Chemistry of the A. M. A. published a review of the subject.²⁰ Compiled in this paper is a table of cases of barbiturate poisoning including those treated with picrotoxin and those not thus treated. As much of the Council data are taken from unpublished reports, it is difficult to correlate the table with that included in our paper. Nevertheless, in the Council table of cases of barbiturate poisoning treated with picrotoxin with recovery there appear to be 10 additional cases that should be added to those we have compiled. These include one case of poisoning with barbital 8.0 gm. (120 grains); three cases with sodium amytal 6.0 to 9.0 gm. (90 to 144 grains); one case with dial 7.6 gm. (115 grains); three cases with phenobarbital or its sodium salt 5.0 to 6.0 gm. (75 to 90 grains); and two cases with sodium pentobarbital 4.0 to 4.75 gm. (60 to 72 grains).

An additional series of cases of barbiturate poisoning not treated with picrotoxin is cited to indicate that "patients may recover, with the prevailing forms of supportive treatment, from doses of barbiturates within the general range of those in which picrotoxin was held responsible for the survival." Among these must be mentioned the cases of Eggers²¹ which survived doses of barbital varying from 15 to 20 gm. (225 to 300 grains) without treatment with picrotoxin. These cases indicate again the difficulty in attributing the recovery of our Case 1 from 16.3 gm. (245 grains) of barbital to picrotoxin. An analysis of the cases treated and untreated (in respect to picrotoxin) revealed no significant differences in symptomatology in barbital poisoning which would indicate with certainty a fatal outcome; nor did the comparison afford evidence of a conspicuous increase in the speed of recovery in the picrotoxin treated cases. Insufficient numbers of cases were available for conclusions as to the effect of picrotoxin on the mortality rate.

The comment of the Council is quoted verbatim as follows: "As matters stand, there seems to be no room for doubt that picrotoxin causes signs of stimulation in human cases of severe barbiturate poisoning. Although there are indications that picrotoxin may enable a patient to survive during barbiturate poisoning that might result fatally with the customary supportive treatment alone, proof that this is so cannot yet be said to have been supplied by the prevailing reports. In the literature there are cases of barbiturate poisoning in which picrotoxin was not used, which are comparable to the picrotoxin-treated cases with respect to dose of the barbiturate, the severity of the poisoning, the duration of the unconsciousness, and the mortality rate. An analysis of the objective factors by which treated and control cases can be compared reveals, therefore, no conspicuous advantage in the picrotoxin treatment. However, the experimental basis for the efficacy of picrotoxin in barbiturate poisoning is fairly strong, and since the objective criteria are not adequate for a final conclusion, the favorable impressions obtained by various authors in individual cases merit consideration. The cautious use of picrotoxin in barbiturate poisoning would, therefore, seem justifiable in cases which can be carefully studied, with the view that they may supply sufficient accurate data from which the proper place of picrotoxin as an antidote may be established."

In March 1939, Dille²² reviewed the pharmacology and clinical use of picrotoxin in barbiturate poisoning, and included in tabular form some of the data found in our table. He concluded: "Pharmacologically, picrotoxin is almost a pure medullary stimulant which makes it of special value in the treatment of poisoning from barbiturates, where death results from the depression of the medullary centers. Clinical

* November 30, 1939.

reports seem to indicate its usefulness under practical conditions. It should, however, be used subject to certain restrictions. First, there should be a definite diagnosis of barbiturate poisoning; second, it should be used only where the degree of poisoning is severe; third, it should be given in divided doses governing the rate of administration and the amount by the needs of the patient; fourth, other measures such as gastric lavage, oxygen and parenteral fluids should be carried out." In regard to the definite diagnosis of barbiturate poisoning, attention should be called to the report of Delmonico.²³ He reviewed the tests for barbituric acid and devised a modification of the Koppanyi test¹ which can be performed on urine without elaborate apparatus within 20 minutes. The rapidity and ease with which this test can be made will aid in the detection of short acting barbiturate compounds, which are unstable and therefore must be tested for immediately by a quick process. The fact that the examination of the urine specimens in our Case 2 was delayed for several days may account for the inability to detect traces of the barbiturate, seconal, which is a quick-acting and unstable compound.

In April 1939, Stephens and Anderson²⁴ reported a case of barbiturate intoxication treated with picrotoxin. The patient, a woman aged 20, ingested 4.75 gm. (72 grains) of sodium amytal with suicidal intent; and was admitted to the hospital 45 minutes later in a comatose state with signs of marked anoxemia, cyanosis, reduced respirations and clonic convulsions. She was treated for 12 hours with strychnine, caffeine, heat and intravenous infusions of 5 per cent glucose in normal saline without favorably influencing her condition. At this time picrotoxin became available and was administered in doses of 6 to 9 mg. intravenously at intervals of 15 to 60 minutes over a period of 24 hours. (One dose of 18 mg. was given.) In this period a total of 156 mg. of picrotoxin was employed. Supportive treatment with oxygen through nasal catheter, strychnine, caffeine, intravenous glucose infusions totalling 6,000 c.c., 50 c.c. of 50 per cent sucrose, and external physical stimulation was continued throughout the period. At the end of 36 hours after the ingestion of the barbiturate the patient regained consciousness and the picrotoxin was discontinued: after 54 hours she was sitting up in bed, eating and rational. She made an uneventful recovery.

In May 1939, Cardle and Hagen²⁵ reported a case of intoxication with 4.0 gm. (60 grains) of phenobarbital treated with picrotoxin. The patient, a woman aged 24, had been without treatment for about 12 hours prior to admission. She was comatose, with slow shallow respirations, slight cyanosis, and diminished reflexes. Gastric lavage, intravenous infusion of 10 per cent glucose in normal saline and caffeine were administered during a period of 9 hours without effect. Picrotoxin was then administered intravenously in doses beginning at 1 mg. and increasing every 20 minutes up to 6 mg. Then 9 to 12 mg. were given every 2 to 4 hours. A total of 147 mg. of picrotoxin was administered in a period of 36 hours: at which time deep reflexes had returned, and the patient was much improved. Consciousness apparently returned, about 57 hours after the ingestion of the phenobarbital, at which time the patient verified the dose taken. She recovered without further incident.

In June 1939, Smyth²⁶ presented the report of a man in his late fifties who ingested 7.4 gm. (112 grains) of phenobarbital, while in a state of depression, and was admitted to the hospital six to eight hours later. At that time he was comatose and markedly cyanotic, with congested lungs, and diminished reflexes. Picrotoxin was not available for use for 12 hours during which large doses of metrazol, coramine, caffeine, strychnine, intravenous infusions of 5 per cent glucose, and 50 per cent sucrose were administered with indifferent results. The administration of picrotoxin was begun approximately 20 hours after the phenobarbital had been ingested, and in a period of 20 minutes, 60 mg. of picrotoxin as 20 c.c. of 0.3 per cent solution were given intravenously. The effects were immediate and striking: the signs of pulmonary edema decreased, respiration became less labored; muscle twitching occurred,

and the patient opened his eyes and asked for water. Thereafter, the state of narcosis gradually lifted. In about four hours another 30 mg. of picrotoxin was given, with more sucrose solution. Approximately 25 hours after the ingestion of the phenobarbital the patient was fully awake and rational, having received a total of 90 mg. of picrotoxin. The patient developed a lung abscess in the right lower lobe, which eventually was drained by rib resection. He was discharged about two months later in good health.

It is to be noted that all of these three patients ingested as much as or more than the usually fatal dose of the barbiturate taken. Attention must be called also to the fact that in each instance much valuable time was wasted in attempting to locate a supply of picrotoxin. Inasmuch as the properly supervised use of the drug is now approved by the Council on Pharmacy and Chemistry of the A. M. A., it seems highly desirable that medical schools and approved hospitals equip themselves with adequate supplies of this important drug in order to be prepared for barbiturate poisoning emergencies.

In September 1939, Lovibond and Steel²⁷ of London reported the case of a woman aged 35 who ingested an unknown quantity of an unknown barbiturate approximately 24 hours before she was admitted to the hospital for treatment. At that time she was in deep coma, with stertorous breathing, slight cyanosis and depressed reflexes. For three hours she was treated with gastric lavage, lumbar puncture, intravenous saline and intranasal oxygen without significant change in her condition. Then picrotoxin was administered intravenously in divided doses of 6 mg. each (2 c.c. of 0.3 per cent solution). There was such a prompt response that after three hours of this treatment (when a total of 42 mg. of picrotoxin had been administered) the patient had recovered sufficiently to ask for water and to hold the glass while she drank. Thereupon picrotoxin was discontinued, and 4 c.c. of coramine were injected intravenously at 2 hour intervals. The patient gradually lapsed again into coma, and 10 hours after the last dose of picrotoxin three more injections of picrotoxin were given during one half hour. Within three hours the patient had regained consciousness, and thereafter made an unevenful convalescence. A total of 54 mg. of picrotoxin and 112 c.c. of coramine were administered.

This case illustrates further the necessity for persistent and prolonged treatment with picrotoxin. Had this drug been continued in small doses at frequent intervals, this patient probably would not have relapsed after responding so satisfactorily to the initial period of treatment.

Summary. To the 24 cases of barbiturate poisoning treated with picrotoxin tabulated in the original communication, this supplementary note appends 14 additional cases, making a total of 38 cases thus treated. A review of these additional data further substantiates the contention that picrotoxin is effective in acute barbiturism, frequently when other measures have failed.

REFERENCES

1. KOPpanyi, T., MURPHY, W. S., and KROP, S.: Colorimetric determination of barbital and its applications, *Proc. Soc. Exper. Biol. and Med.*, 1933, xxx, 542-544.
2. ARNETT, J. H.: Ephedrine and picrotoxin used successfully in amytal poisoning, *Jr. Am. Med. Assoc.*, 1933, c, 1593.
3. MURPHY, W. S., CONNERTY, H. V., CONNOLLY, A. J., and KOPpanyi, T.: Studies on barbiturates. XVI. Barbiturate poisoning treated with picrotoxin, *Jr. Lab. and Clin. Med.*, 1937, xxii, 350-356.
4. VOLPITTO, P. P.: Picrotoxin as an antidote in acute poisoning from barbituric acid derivatives, *Trans. Am. Soc. Anesth.*, New York (April 8), 1937. (Unpublished) Copy furnished through courtesy of Dr. Paul M. Wood, Secretary, Am. Soc. Anesth., New York.

5. BURSTEIN, C. L., and ROVENSTINE, E. A.: Clinical experience with newer analeptics, *Curr. Res. Anes. and Anal.*, 1937, xvi, 151.
6. COHEN, S. J., and KOHN, R.: The use of picrotoxin as an antidote for luminal poisoning, *Jr. Pharmacol. and Exper. Therap.*, 1937, ix, 102-103.
7. KLINE, E. M., BIGG, E., and WHITNEY, H. A. K.: Picrotoxin in the treatment of barbiturate poisoning. Report of case, *Jr. Am. Med. Assoc.*, 1937, cix, 328-330.
8. McDANIEL, F. L., and BELL, R. A.: Barbiturate poisoning. A review with report of two cases, *U. S. Naval Med. Bull.*, 1938, xxxvi, 32-43.
9. ROVENSTINE, E. A.: The antidotal action of picrotoxin in acute intoxication by the barbiturates, *Am. Jr. Med. Sci.*, 1938, cxcvi, 46-50.
10. KOHN, R., PLATT, S. S., and SALTMAN, S. Y.: The picrotoxin-barbiturate antagonism. Clinical observations, *Jr. Am. Med. Assoc.*, 1938, cxi, 387-390.
11. BLECKWENN, W. J., and MASTEN, M. G.: The antidotal treatment of barbiturate intoxication. Report of treatment with picrotoxin in six cases, *Jr. Am. Med. Assoc.*, 1938, cxi, 504-507.
12. WEISS, S.: The indications and dangers of sedatives and hypnotics with special reference to the barbituric acid derivatives, *Internat. Clin.*, 1936, i, 39-66.
13. FANTUS, B.: Therapy of barbiturate poisoning, *Jr. Am. Med. Assoc.*, 1934, ciii, 749-750.
14. PURVES-STEWART, J., and WILLCOX, W.: Cisternal drainage in coma from barbitone poisoning, *Lancet*, 1934, i, 500-503.
15. SOLLMANN, T.: A manual of pharmacology and its applications to therapeutics and toxicology, 5th Ed., 1936, W. B. Saunders Company, Philadelphia, p. 737.
16. UNDERHILL, F. P.: Toxicology, or the effects of poisons, 3rd Ed., 1936, Blakiston, Philadelphia, p. 250.
17. PURVES-STEWART, J., and WILLCOX, W.: Poisoning by barbitone and allied drugs, *Lancet*, 1934, i, 6.
18. CHANG, D. K., and TAINTER, M. L.: Unusual case of barbital poisoning with recovery, *Jr. Am. Med. Assoc.*, 1936, cvi, 1986.
19. BERTRAND-FONTAINE, MME., and CLAASS, M. A.: Intoxication par une dose massive de véronal. Traitement strychnique intensif. Guérison, *Bull. et mém. Soc. méd. hôp. de Paris*, 1933, xlix, 1177.

SUPPLEMENTARY REFERENCES

20. Report of the Council on Pharmacy and Chemistry: Present status of picrotoxin in poisoning by the barbiturates, *Jr. Am. Med. Assoc.*, 1939, cxii, 431-433.
21. EGGERS, P.: Eine schwere Veronal-Vergiftung, *Samml. v. Vergiftungsfallen*, 1938, ix, 31.
22. DILLE, J. M.: Picrotoxin. Its pharmacology and clinical use in barbiturate poisoning, *Northwest. Med.*, 1939, xxxviii, 80-83.
23. DELMONICO, E. J.: Tests for derivatives of barbituric acid, *Proc. Staff Meetings Mayo Clinic*, 1939, xiv, 109-112.
24. STEPHENS, J. T., and ANDERSON, J. P.: Picrotoxin in the treatment of barbiturate intoxication, *Ohio State Med. Jr.*, 1939, xxxv, 396-397.
25. CARDLE, A. E., and HAGEN, W. S.: Picrotoxin treatment of barbiturate intoxication, *Minnesota Med.*, 1939, xxii, 310.
26. SMYTH, L. A.: A case of barbiturate poisoning treated with picrotoxin, *Jr. Med.*, 1939, xx, 160-162.
27. LOVIBOND, J. L., and STEEL, G. C.: Picrotoxin in the treatment of barbiturate poisoning, *Lancet*, 1939, ii, 561-562.

THE EFFECT OF GASTRECTOMY ON THE MONKEY *

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THE etiology of pernicious anemia is an unsolved problem. Until this disease can be produced experimentally the etiology will probably remain uncertain.

The almost constant presence of achylia gastrica in this disease and the series of experiments by Castle and his associates ⁶ suggest that a gastric disorder plays a primary rôle in the pathogenesis of pernicious anemia. Complete removal of the stomach from animals should provide experimental evidence relating to such an hypothesis.

The entire stomach of various types of adult animals [dog ^{1, 4, 7, 9, 16, 20, 25, 29a, 34, 37, 43}; cat ⁵; rat ^{3b, 21}; pig ^{2a, 2b, 3c, 13, 24, 29b}; monkey ¹¹] has been removed by several groups of investigators; but, with two possible exceptions [rat ^{3b} and pig ^{2b}], pernicious anemia has not been produced experimentally. Since the monkey stands closest to man in the evolutionary scale, we have studied the long-time effects of gastrectomy on this animal. A preliminary report of hematologic studies has been published.^{3a} The completed studies are recorded in this paper together with the results of feeding a Wills diet.^{42b}

OPERATIVE METHODS

Eight (5 females and 3 males) of a group of 10 *Macacus rhesus* monkeys, averaging 10 pounds in weight, were gastrectomized; two (1 male and 1 female) were retained as controls. The animals were observed for at least one month prior to operation during which period normal blood findings were recorded.^{3a} The monkeys were young, but their exact age was unknown. At operation the entire stomach was removed. An end-to-end anastomosis between the esophagus and duodenum was then made. From 100 to 200 c.c. of saline were given by hypodermoclysis immediately after closing the abdomen. On the second postoperative day the monkeys were given sugar water by mouth in small amounts. On subsequent days the amounts of water were gradually increased, and milk, bananas, boiled potatoes, bread and a little meat were gradually added to the diet until the animal was eating as before.

POSTOPERATIVE COURSE

Two of the gastrectomized monkeys (numbers 3 and 5) died of peritonitis within a period of three weeks following the operation. Monkey

* Received for publication January 30, 1939.

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number 2 slowly lost weight following the operation and died of tuberculosis 187 days later. The postoperative course of the five surviving gastrectomized monkeys is briefly summarized in table 1.

TABLE I

Monkey No.	Wt. lbs. at operation	Postoperative weight		Weight at death	
		Days post-operative			
		Days	lbs.	Days	lbs.
1, female	5.5	594	8	937	5.0
6, female	14.5	736	13	845	8.0*
7, male	8.0	243	7.3	478	5.0
8, female	10.2	267	10.0	843	4.75*
9, female	8.5	594	9.5	695	7.0*

* Gastrectomized monkeys 6, 8, and 9 were fed a Wills diet which accounts for their loss of weight and death.

It is to be noted that the five monkeys survived from 478 to 937 days. They would have survived longer had they not been used for certain experiments. *None of them developed the blood picture of pernicious anemia as seen in man.*

HEMATOLOGIC PROCEDURES

Blood examinations, consisting of red blood cell count, hemoglobin by the Newcomer method, hematocrit,³¹ and Price-Jones determinations of mean cell diameter by direct measurement on blood smears stained with Wright's stain, were made every 30 days.

The blood picture for 11 normal monkeys is shown in table 2.

TABLE II

Determination	Number of determinations	Mean	Range
R.B.C. (red blood count in millions).....	24	6.20	4.72- 7.66
Hb (hemoglobin in grams per 100 c.c.).....	24	12.86	9.00-17.27
Hematocrit (Rosahn).....	24	47.64	39.00-55.75
Price-Jones count (micra).....	23	7.04	6.79- 7.75

CLINICAL COURSE OF THE GASTRECTOMIZED MONKEYS

First Year Post-Operative. The blood pictures of the gastrectomized monkeys varied slightly. For about 180 days following the operation they showed a mild oligocythemic, hypochromic, normocytic anemia. Two monkeys (numbers 6 and 8), slightly more anemic than the others, were given 0.1 gram of iron citrate subcutaneously every other day for one month. Their blood pictures returned to normal (table 3).

Second and Third Years Post-Operative. One year following the opera-

TABLE III

Treatment (16 injections)	Monkey	Weight	D.P.O.*	R.B.C.	Hb	Hemato- crit	Price- Jones
Before	#6	12	173	4.90	9.95	37.50	6.86
After	#6	12½	205	6.06	13.49	43.00	6.52
Before	#8	9	124	4.52	8.36	30.50	6.82
After	#8	8¾	156	5.96	12.30	41.25	7.12

* D.P.O.: days post-operative.

tion the blood picture varied with the different animals. Monkey number 1 showed no deviation from a normal blood picture at any time. Monkey number 6 developed a moderate hyperchromic anemia which did not respond completely to injections of iron citrate or to injections of liver extract of established potency. The anemia disappeared spontaneously, although hyperchromia persisted (table 4).

TABLE IV

Treatment	Weight	D.P.O.*	R.B.C.	Hb	Hemato- crit	Price- Jones
Monkey 6						
Iron citrate subcutan.	11	460	3.84	9.05	32.75	7.40
Total—1.2 grams	10	490	4.87	10.20	36.00	7.39
Chappel's concentrated liver extract—9 c.c.	10¼	520	4.70	11.61	40.00	7.44
No therapy	12	578	5.30	13.14	43.00	—

* D.P.O.: days post-operative.

After the study on monkey number 6 (table 4) was made, she became pregnant, the pregnancy being first diagnosed 716 days post-operative. A full term female fetus was born with the membranes unruptured and the placenta intact (765 d. p. o.). The fetus died soon after the membranes were artificially ruptured. *Although this animal did not develop an anemia of pregnancy, an anemia did occur during the puerperium.* No postpartum hemorrhage occurred. The blood picture before and after parturition is shown in table 5.

Monkey number 7 developed a normocytic, mildly macrocytic anemia 418 days post-operative. The animal was given injections of ferric citrate and then injections of liver extract of established potency. An edema of the face occurred after the first injection of liver extract. The edema became progressively worse and the animal was sacrificed for autopsy one month later. The liver extract did not significantly affect the anemia and the macrocytosis (table 6).

TABLE V

Days ante- or post-partum	Weight	D.P.O.	R.B.C.	Hb	Hemato-crit	Price-Jones
Monkey 6						
173 a. p.	12	592	5.08	12.90	43.50	—
49 a. p.	12 $\frac{1}{4}$	716	5.40	14.93	51.25	—
29 a. p.	12 $\frac{1}{4}$	736	5.42	14.12	44.50	—
4 a. p.	11 $\frac{1}{2}$	761	5.34	12.44	44.50	7.50
Term		765				—
3 p. p.	—	768	3.74	10.67	37.50	7.52
32 p. p.	8 $\frac{1}{2}$	797	4.88	10.40	36.00	7.86

TABLE VI

Treatment	Weight	D.P.O.	R.B.C.	Hb	Hemato-crit	Price-Jones
Monkey 7						
Iron citrate subcutan.	5 $\frac{3}{4}$	418	4.86	10.20	39.75	7.89
Total—1.3 grams	5	448	4.82	9.50	34.00	7.62
Chappel's concentrated liver extract—7.5 c.c.	5	463	4.45	8.54	31.00	8.10
	5	478	5.75	10.10	34.75	8.00

Blood was taken and the animal killed for autopsy specimens on the 478 D.P.O.

Monkey number 8 developed a moderate hypochromic anemia 411 days post-operative. This anemia responded to ferric citrate injections, but liver extract increased the number of red blood cells but not the hemoglobin. The anemia was aided most by a combination of iron and liver extract. The results are illustrated by the data in table 7. At 632 days post-operative, a normocytic anemia developed which did not respond to liver extract.

Monkey number 9 developed a moderate normochromic anemia from

TABLE VII

Treatment	Weight	D.P.O.	R.B.C.	Hb	Hemato-crit	Price-Jones
Iron citrate subcutaneously	9 $\frac{1}{2}$	411	5.36	10.25	37.75	7.47
Total—1.25 grams	8 $\frac{1}{4}$	441	5.21	12.31	39.00	7.48
	8	456	5.68	13.31	43.75	—
Lederle's concentrated liver extract—4 c.c.	8 $\frac{1}{2}$	486	4.40	11.30	37.25	—
	9 $\frac{1}{4}$	515	5.58	11.80	42.00	—
Iron citrate—0.65 gram	9 $\frac{1}{2}$	529	5.30	12.59	43.50	7.39
Liver extract—3 c.c.	9 $\frac{1}{4}$	543	6.05	14.12	47.75	7.25
	9	564	5.55	13.49	44.00	—

time to time. This anemia would disappear without treatment and was not affected by either liver extract alone or liver extract and iron injections.

EFFECT OF THE WILLS DIET

In 1935 Wills and Stewart^{42b} described a macrocytic, hyperchromic anemia in monkeys which occurred when the animals were fed a diet similar to the diet of Mohammedan women patients in Bombay.^{42a} This diet consisted of polished rice, 40 parts, and margarine, 15 parts, cooked together by boiling, salt added to flavor, and then white bread, 45 parts, mixed with the rice-margarine-salt mixture. In addition to this diet, each monkey was given a 25 gram portion of tomato or carrot and 3 c.c. of cod liver oil daily. After feeding this diet for about one month, we decided that the white bread referred to by Wills^{42b} must have been a native variety. The diet was modified accordingly and unleavened bread was substituted for the white bakery bread. In place of the sodium chloride we substituted McCollum's salt mixture²⁸ minus the iron. Since we were using large quantities of this diet not only for monkeys, but also for pigs, dogs, and rats, large batches were prepared at one time.

This diet was fed to gastrectomized monkeys number 8 and number 9 and to one normal monkey number 40. The diet, along with 5 grams daily of autolyzed yeast extract (Marmite or Vegex), was fed to gastrectomized monkey number 6 and to a normal monkey number 41.

The normal and the gastrectomized monkeys survived on this diet only from 41 to 152 days, although Wills^{42b} reported that a similar diet fed with 5 grams of Marmite daily would maintain monkeys for 18 months. Young rats would survive on the diet [Marmite (5 per cent) was given], but would not grow nearly so well as litter-mates fed our laboratory stock-diet.

None of the monkeys on the Wills diet developed pernicious anemia. The measurements of the diameter of the red cells showed that some macrocytosis was present. The animals became emaciated and the injection of liver extract did not improve their blood picture or their nutritional state (table 8). Monkey number 9, however, while on the diet exhibited very marked hyperplasia of the bone marrow.

TABLE VIII
Antemortem Data on the Monkeys on the Wills Diet

Monkey	Treatment	Days post-operat.	Days on diet	Weight (pounds)	R.B.C. millions	Hb (in grams) per 100 c.c.	Hemato-crit	P. J. (Price-Jones)	Days on diet until death
Gastrect. No. 6	5 grams of Vegex daily	837	33	8½	4.13	8.85	31.50	7.93	41
Normal No. 10	5 grams of Vegex daily	0	112	5½	6.28	11.30	40.00	7.49	152
Gastrect. No. 8	Liver extract	820	65	5½	4.25	9.01	34.00	7.73	88
Gastrect. No. 9	None	688	51	7	5.10	10.05	35.00	7.61	58
Normal No. 41	None	0	96	4	4.46	8.76	37.50	—	99

CAUSE OF DEATH AND MICROSCOPIC STUDIES

It is to be recalled that monkeys 3 and 5 succumbed to postoperative peritonitis.

The bone marrow of *several normal monkeys* was studied. It may be described very briefly as follows:

Head of femur: Entirely fatty marrow.

Lower end of femur: Entirely fatty marrow.

Mid-femur: Cellular marrow interspersed with fat vacuoles which occupy from 30 to 90 per cent of the area of the transverse section. Erythrocytic cells, especially normoblasts with a few macronormoblasts intermingled, strongly predominate. Undifferentiated cells, myelocytes, and young forms of polymorphonuclears in the usual proportions.

Vertebral marrow: Moderately dense, cellular marrow interspersed with large and small fat vacuoles which occupy approximately 10 to 30 per cent of the area represented by the sections. The cells are predominantly granulocytes and undifferentiated cells, but with an almost equal number of erythrocytic cells in some unevenly distributed areas.

Gastrectomized Monkey Number 1. This monkey survived 937 days after operation and, although small at the start, lost 0.5 lb. of weight. The animal was sacrificed and the description of the bone marrow follows: Bone marrow, mid-femur: The marrow is generally hyperemic; both the larger and smaller blood channels are widely dilated. Practically all fat has been replaced by a mucoid substance and the marrow is not as compactly arranged as normal marrow. To a small extent the marrow cells are scattered through the mucoid matrix. Compact masses of brown, coarsely granular pigment are scattered throughout the marrow and appear to be both extra- and intra-cellular. The cells, as nearly as can be ascertained from formalin fixed H. and E. sections, consist largely of undifferentiated cells and cells of the erythrocytic series. Eosinophilic myelocytes and metamyelocytes are present but very scarce. The reticulum cells, because they enmesh the mucoid matrix, are unusually prominent. In a few areas they have proliferated and formed fairly dense masses of the one type of cell. In other areas of similar size or larger the cells are composed almost entirely of small lymphoid cells; but, in general, the cellular marrow consists of mixtures of cells—hemocytoblast-like cells, histiocytes, monocytoïd cells, erythroblasts, and normoblasts. Cells with complex nuclei, or with multiple nuclei, and with more or less abundant, irregular cytoplasm are unusually numerous. These resemble immature as well as fully mature megakaryocytes. A few have pyknotic nuclei. Occasionally a hemoglobin-containing giant form with a small spherical nucleus (megaloblast) is found among the normoblasts.

Gastrectomized Monkey Number 2. This animal died of generalized tuberculosis 187 days after gastrectomy. The description of the bone marrow follows: Bone marrow, mid-femur: This resembles the marrow of number 1 with the exception that histiocytes and, to a slighter extent, eosinophiles are relatively more numerous. There are no fat vacuoles, but the mucoid appearance of the stroma seen in number 1 is lacking. This is due, in part, to the diffuse scattering of histiocytes in the stroma. (The presence of tuberculosis, previously mentioned, is sufficient to account for the histiocytic hyperplasia of the marrow.)

(Monkeys numbers 3 and 5 died of peritonitis and number 4 was a control.)

Gastrectomized Monkey Number 6. This animal died of nutritional cachexia due

to the Wills diet (845 days post-operative). The essential microscopic findings were: Bone marrow, mid-femur: This marrow is more cellular than that of number 1, but in other respects, i.e., in the absence of fat, presence of mucoid stroma, engorgement of blood channels and distribution of cell types, it is essentially similar. Normoblasts are relatively more numerous. The discs of femoral marrow (cross section) are more cellular at the periphery and less cellular, with mucoid appearance of the stroma, in the centers. The deposits of brown pigment are less abundant than in number 1. Liver: Moderate parenchymatous degeneration and slight pigmentation (brown granular pigment) of the Kupffer cells. Spleen: Moderately heavy pigmentation of the littoral cells; otherwise normal.

Gastrectomized Monkey Number 7. This is the animal that developed edema of the face, limbs and genitalia after the administration of liver extract. Nothing was found at autopsy (478 days post-operative) to account for the edema. Bone marrow, mid-femur: The degree of cellularity is much reduced from the normal with a corresponding increase of mucoid matrix, especially in the center of the marrow cylinder. Bone marrow, vertebra: The marrow cells are arranged in thin strands and small clumps and it is estimated that about 10 per cent or less of the area represented by the sections is composed of cells; the rest is mucoid matrix. No fat vacuoles are present. Lungs: There are areas of thickened trabeculae and alveolar septa alternating with areas of saccular emphysema, evidence of old healed inflammatory foci, but no evidence of recent pneumonitis. Kidney: Essentially normal. Adrenal: Essentially normal. Liver: There are a few minute, widely scattered foci of necrosis and leukocytic infiltration. Otherwise, the tissue is essentially normal. Spleen: The phagocytic cells of the sinusoids contain a large quantity of granular, golden brown pigment; otherwise the tissue appears normal.

Gastrectomized Monkey Number 8. This animal died (sacrificed) of nutritional cachexia due to the Wills diet (843 days post-operative). It received liver extract before death. The essential microscopic findings were: Bone marrow: The marrow is rather poor in cells; fat vacuoles are not recognizable. The mucoid appearance of the stroma observed in the other animals of this series is not present. Small groups of normoblasts are easily recognizable, and erythroblasts appear to be present in the usual proportion. The other cells are chiefly of the granulocytic series which definitely predominate in these sections. The only definite alterations from normal are the loss of fat associated with loose arrangement of the marrow cells and a general reduction in the number of marrow cells. Heart: Mild parenchymatous degeneration. Liver: Mild parenchymatous degeneration. Spleen: No noteworthy findings.

Gastrectomized Monkey Number 9. This animal died (sacrificed) of nutritional cachexia due to the Wills diet (695 days post-operative). It had received neither Marmite nor liver extract prior to death. The essential microscopic findings were: Bone marrow, mid-femoral (biopsy, 635 days post-operative: before Wills diet): This fragment contains strands of marrow cells interspersed with fat vacuoles, in contrast with the sections from the autopsy specimen. Bone marrow, mid-femoral autopsy specimen (695 days post-operative: after Wills diet): All sections show solidly cellular marrow in which neither vacuoles nor mucoid stroma appear. The sinusoids are narrow, but well filled with blood. Undifferentiated cells with vesicular, oval or indented nuclei, resembling hemocytoblasts, far outnumber all other cells. Among these are numerous mitotic figures. Multinucleated cells with nuclear structure resembling that of hemocytoblasts are present in large numbers. Many of these reach the size of megakaryocytes. Amorphous golden brown or greenish brown pigment in coarse clumps is present in large quantity. Eosinophiles are much fewer than usual. Cells of the erythrocytic series are very few; normoblasts occur singly and in small clumps. Macrophages are moderately numerous and can be distinguished readily by their large content of brown pigment. In several places there are large and small,

poorly outlined masses of small lymphocytes. The most conspicuous features of this marrow are: (1) the great proliferation of undifferentiated cells (hemocytoblasts); and (2) the excessive quantity of pigment (presumably blood pigment). Bone marrow, head of femur: Poorly cellular, fatty marrow; but, as compared with a normal marrow from this location, this represents a significant hyperplasia. Liver: There is a fairly prominent deposit of brown pigment in the Kupffer cells. Spleen: Moderate diffuse engorgement of the pulp, but relatively scanty quantities of pigment.

Normal Control Monkey Number 40 on the Wills Diet. This animal died of nutritional cachexia due to the Wills diet. Bone marrow, mid-femur: Widely dilated blood-filled sinusoids. Fat vacuoles occupy approximately 10 to 20 per cent of the area represented by the sections. There is diffuse hyperplasia of undifferentiated large basophilic cells resembling hemocytoblasts, neutrophilic myelocytes, and metamyelocytes with suppression of the erythroblastic elements. Foci of nucleated erythrocytes are extremely small and few. A moderate number of mature neutrophils, eosinophilic myelocytes, and metamyelocytes are present in the tissue. Normal megakaryocytes are especially numerous. (This is a markedly hyperplastic marrow involving chiefly the stem cells, with a tendency to differentiation in the direction of granulocytes, i.e., a leukemoid picture. F. D. Gunn.)

Normal Control Monkey Number 41 on the Wills Diet with Marmite. This animal died of nutritional cachexia, but in addition it had a colitis and non-suppurative epiphysitis of one femur. Bone marrow, mid-femur: This is a diffusely hyperplastic marrow with distended, well filled sinusoids and nearly complete obliteration of fat vacuoles. Granulocytes are much increased in number at the expense of the erythrocytic series of cells. Neutrophilic myelocytes, metamyelocytes and young segmented predominate. Mitotic figures are moderately numerous among the myelocytes. Eosinophilic myelocytes and mature eosinophiles appear in relatively small numbers (5 to 10 per oil immersion field). The few remaining megakaryocytes show pyknosis and karyorrhexis of their nuclei and advanced degeneration of their cytoplasm. Foci of erythroblastic cells are small and widely separated. Normoblasts are fewer than normal and scattered unevenly among the marrow cells. They show a few abnormal forms (lobulated nuclei, cytoplasmic inclusions and occasional cells with giant cytoplasm) but in general there is no significant alteration of the cells of the erythrocytic series. Small masses of bacteria, some of which have been phagocytized, are found in many places. They have the form of small short bacilli and diplococci. Spleen: Very mild swelling and hyperplasia of the littoral cells. Adrenal: Essentially normal. Liver: Moderate granular degeneration and disorganization of cells of the liver cords. (This may be accounted for in part by postmortem alteration.) Thyroid gland: Essentially normal. Colon: The mucosa is seminecrotic, the glands are disorganized and in places the membrane is ulcerated down to the *muscularis mucosae*. The leukocytic infiltrate is confined to the mucosa and consists chiefly of polymorphonuclear neutrophils. Microscopic diagnosis: Acute ulcerative colitis. Infectious hyperplasia of the bone marrow. Slight septic splenitis. Parenchymatous degeneration of the liver.

DISCUSSION

Goldhamer¹¹ reported that after gastrectomy in monkeys a "secondary" type of anemia appeared and persisted. The specific blood picture of pernicious anemia did not develop within his six-month period of study. Our work confirms this finding. We can say, further, that pernicious anemia did not develop in gastrectomized monkeys within a period of approximately three years.

Since gastrectomy alone did not produce pernicious anemia in monkeys, one should examine more closely the theory of the metabolism of the anti-pernicious anemia substance which has arisen from the observations and conclusions of Castle⁶ and many other workers. An extrinsic factor, *A*, present in certain foods, reacts with an intrinsic factor, *B* (presumably an enzyme) present in normal human gastric juice, to form an anti-pernicious anemia substance, *C*, which is absorbed from the intestine, *D*, stored in the liver, *E*, and released from the liver, *F*, to the bone marrow, *G*, for utilization when needed. Theoretically a disturbance of this mechanism at any of the points *A*, *B*, *C*, *D*, *E*, *F*, or *G* may produce a macrocytic anemia.

Greenspon¹⁴ and Morris²⁷ have denied the necessity of an extrinsic factor; but their conclusions have apparently been disproved.^{15, 18, 61, 17, 40, 41, 10}

Is the Stomach the Sole Site of Formation of Intrinsic Factor? Remissions of pernicious anemia have been produced by the oral administration of desiccated duodenum^{35, 26a} and colon,³³ as well as desiccated stomach.^{39a, 35, 20b, 19} The activity of desiccated stomach and duodenum has been explained on the basis of a postmortem reaction between intrinsic and extrinsic factors present in the mucosa and muscle wall.^{39b} Proof of anti-pernicious anemia potency of a portion of the gastrointestinal tract, however, does not permit the presumption that these active portions are the site of formation of intrinsic factor. The gastric lesion (upper two-thirds of the stomach) in pernicious anemia²³ does not coincide with the portions of the gastrointestinal tract (pylorus,^{20b, 26c} duodenum^{35, 26a} and colon³³) found to be active in the treatment of pernicious anemia. And, Castle^{6h} denies that intrinsic factor is present in duodenal contents from which gastric juice has been excluded.

If the gastric juice is the sole source of intrinsic factor, then gastrectomy, according to the metabolic theory outlined above, should produce pernicious anemia. Since gastrectomy did not produce pernicious anemia, either the stomach is not the sole source of intrinsic factor or the simple loss of intrinsic factor in itself will not produce pernicious anemia, or the monkey does not require the anti-pernicious anemia factor. Perhaps the intestinal tract performs a more important function than passive absorption. This seems likely from our results and also in view of the fact that the reaction product of the intrinsic and extrinsic factors has not been definitely identified as the thermostable anti-pernicious anemia factor present in normal liver. Klein and Wilkinson²² claim to have synthesized the active principle of liver in vitro by incubating beef muscle and hog stomach extracts. A relatively thermostable substance extractable by methods used for producing potent liver extract was formed. Castle,^{6h} however, was unable to confirm this observation.

If we assume that the normal intestine utilizes the reaction product of the extrinsic and intrinsic factors to complete the synthesis of the thermostable anti-pernicious anemia factor, and, that in the absence of such a reaction product because of lack of intrinsic factor, the normal intestine is able, to

a limited extent, to carry on the complete process, the results of gastrectomy may be reconciled with the metabolic theory.

Since gastrectomy did not produce pernicious anemia, we placed the additional strain of a Wills deficient diet upon our animals. In 1932, Wills and Billmoria ^{42a} produced in monkeys a macrocytic anemia with megaloblastic hyperplasia of the bone marrow by feeding a deficient diet. It was first postulated that this anemia was due to lack of the extrinsic factor of Castle since the anemia responded so well to feedings of autolyzed yeast (Marmite-Vegex), a potent source of extrinsic factor. Further reports by Wills and her associates ^{42b, 42c} on this macrocytic anemia in monkeys stated that the anemia responded to autolyzed yeast and to liver extract, but not to purified liver extract (anhaemin), and could not, therefore, be due solely to the absence of Castle's extrinsic factor as originally suggested.

That the Wills diet was deficient there can be no doubt; but the addition of autolyzed yeast extract did not make it complete (see section Effect of Wills Diet). Only one gastrectomized monkey (number 9) showed any evidence in the bone marrow of a reversion to a more primitive type of erythropoiesis. These changes were not reflected in the blood picture (table 8). In this animal the changes in the bone marrow were apparently not the result of gastrectomy alone (see data above on Bone Marrow Biopsy and Autopsy Specimens), but the result of gastrectomy plus the Wills diet. Injections of potent liver extract in gastrectomized monkey number 8 caused no reticulocyte response and no improvement in the blood picture. No other studies could be carried out because all of the animals died before anemia of any severity developed. It was unfortunate that this diet proved so unsatisfactory. Since operative intervention has thus far failed, the line of attack through diet seems to afford the greatest hope for the future solution of the problem of the etiology of pernicious anemia.

In this regard, the work of Rhoads and Miller ³⁰ seems especially significant. Feeding a modified canine black-tongue diet to swine produced a symptom-complex marked by oral mucous membrane lesions, achlorhydria, and anemia (not pernicious anemia). The disease was associated with a loss of the anti-pernicious anemia potency of the gastric juice and liver. Remissions of the anemia and amelioration of the symptoms were induced by oral or parenteral administration of liver extracts.

Gastrectomy in swine also produces a loss of the anti-pernicious anemia potency of the liver ^{2a, 13, 3c} and a hypochromic, microcytic anemia ^{2a, 3c, 24} which does not respond to injections of potent liver extract. Bence ^{2b} reported that gastrectomized pigs which live two to three years after operation develop a blood picture and bone marrow changes like those seen in clinical pernicious anemia. Gastrectomy did not produce this condition in a 2.66 year period in the monkey. Gastrectomy plus a deficient diet was associated with bone marrow changes (hyperplasia of undifferentiated cells) in one monkey. Since the changes in the gastrectomized pig reported by Bence ^{2b}

appeared so long after the stomach was removed, it seems likely that these changes were not due to a simple deficiency of intrinsic factor, but were dependent upon changes in the gastrointestinal tract or hematopoietic system brought on by a deficient diet or deficient intestinal digestion caused by the loss of all of the functions of the stomach.

The occurrence of a pregnancy in one of our gastrectomized monkeys was not associated with anemia except in the puerperium. The absence of an anemia of pregnancy in this gastrectomized monkey does not lend support to the conclusion of Strauss and Castle³⁸ and other authors^{32, 8, 12} that a gastric secretory defect per se is of importance in the development of an anemia of pregnancy.

SUMMARY AND CONCLUSIONS

1. Gastrectomy in monkeys did not produce pernicious anemia in the 2.66 year period of study. (a) Studies on five gastrectomized monkeys are reported. (b) The effects of subcutaneous injections of iron citrate and of liver extract are described. (c) Bone marrow studies are reported. (d) Results of feeding a Wills diet are reported.

2. The bone marrow in one gastrectomized monkey fed a Wills diet showed a great proliferation of undifferentiated cells (hemocytoblasts) and an excessive quantity of pigment. These changes were not reflected in the blood picture.

3. Pregnancy in one of the gastrectomized monkeys was not accompanied by anemia.

4. The etiology of pernicious anemia, with especial reference to the gastric factor, is discussed.

REFERENCES

1. ARON, E., and BAUER, R.: Anémie expérimentale chez le chien. Influence respective de la gastrectomie totale et des dérivations pancréatique, biliaire et duodenale, *Compt.-rend. Soc. de Biol.*, 1933, cxiii, 1065-1067.
2. a. BENGE, J.: Die Rolle des Magens und der Leber in der Pathologie der perniziösen Anämie, *Ztschr. f. klin. Med.*, 1933, cxxvi, 127-142.
b. BENGE, J.: Die Beziehungen der experimentellen agastrischen Anämie zur Perniciosa, *Ztschr. f. klin. Med.*, 1936, cxxx, 275-298.
3. a. BUSSABARGER, R. A., and IVY, A. C.: Hematologic studies on gastrectomized monkeys, *Proc. Soc. Exper. Biol. and Med.*, 1936, xxxiv, 151-152.
b. BUSSABARGER, R. A., and JUNG, F. T.: Dietary and hematologic studies after gastrectomy in the rat, *Am. Jr. Physiol.*, 1936, cxvii, 59-67.
c. BUSSABARGER, R. A., IVY, A. C., and RICHTER, O.: To be published.
4. CARREL, H., MEYER, G. M., and LEVENE, P. A.: The metabolism of dogs with functionally resected small intestine, *Am. Jr. Physiol.*, 1910, xxvi, 369-381.
5. CARVALLO, J., and PACHON, V.: *Arch. de Physiol. norm. et path.*, 1895, vii, 349.
6. a. CASTLE, W. B.: Observations on etiologic relationship of achylia gastrica to pernicious anemia; effect of administration to patients with pernicious anemia of contents of normal human stomach recovered after ingestion of beef muscle, *Am. Jr. Med. Sci.*, 1929, clxxviii, 748-764.

- b. CASTLE, W. B., and TOWNSEND, W. C.: Observations on etiologic relationship of achylia gastrica to pernicious anemia; effect of administration to patients with pernicious anemia of beef muscle after incubation with normal human gastric juice, *Am. Jr. Med. Sci.*, 1929, clxxviii, 764-777.
- c. CASTLE, W. B., TOWNSEND, W. C., and HEATH, C. W.: Observations on etiologic relationship of achylia gastrica to pernicious anemia; nature of reaction between normal human gastric juice and beef muscle leading to clinical improvement and increased blood formation similar to effect of liver feeding, *Am. Jr. Med. Sci.*, 1930, clxxx, 305-335.
- d. CASTLE, W. B., HEATH, C. W., and STRAUSS, M. B.: Observations on etiologic relationship of achylia gastrica to pernicious anemia; biologic assay of gastric secretion of patients with pernicious anemia having free hydrochloric acid and that of patients without anemia or with hypochromic anemia having no free hydrochloric acid, and of rôle of intestinal impermeability to hematopoietic substances in pernicious anemia, *Am. Jr. Med. Sci.*, 1931, clxxxii, 741-764.
- e. CASTLE, W. B., and RHOADS, C. P.: Etiology and treatment of sprue in Porto Rico, *Lancet*, 1932, i, 1198-1199.
- f. CASTLE, W. B., and RHOADS, C. P.: Observations on the etiology and treatment of sprue in Porto Rico, *Jr. Am. Med. Assoc.*, 1932, xcix, 166.
- g. CASTLE, W. B., RHOADS, C. P., LAWSON, H. A., and PAYNE, G. C.: Etiology and treatment of sprue; observations on patients in Puerto Rico and subsequent experiments on animals, *Arch. Int. Med.*, 1935, lvi, 627-699.
- h. CASTLE, W. B.: Etiology of pernicious and other related macrocytic anemias, *Science*, 1935, lxxxii, 159-164.
- i. CASTLE, W. B., and HAM, T. H.: Observations on etiologic relationship of achylia gastrica to pernicious anemia; further evidence for essential participation of extrinsic factor in hematopoietic responses to mixtures of beef muscle and gastric juice and to hog stomach mucosa, *Jr. Am. Med. Assoc.*, 1936, cvii, 1456-1463.
- 7. DAGEW, W. F.: Aenderungen in den Verdauungsprozessen nach Gastroduodenostomie und Gastrojejunostomie, und nach totaler Magenexstirpation, *Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, 1913, xxvi, 176-195.
- 8. DAVIES, D. T., and SHELLEY, U.: Hypochromic anemia and its relation to pregnancy, *Lancet*, 1934, ccxxvii, 1094-1099.
- 9. FONTES, G., KUNLIN, J., and THIVOLLE, L.: Impossibilité de réaliser une anémie à type biermérien par la gastrectomie totale chez le chien, *Compt.-rend. Soc. de Biol.*, 1935, cxx, 1291-1294.
- 10. FOUTS, P. J., HELMER, O. M., and ZERFAS, L. G.: Formation of hematopoietic substance in concentrated human gastric juice, *Am. Jr. Med. Sci.*, 1934, clxxxvii, 36-49.
FOUTS, P. J., HELMER, O. M., and ZERFAS, L. G.: Hematopoietic response to intramuscular injections of concentrated human gastric juice, *Brit. Med. Jr.*, 1934, i, 141-143.
- 11. GOLDHAMER, S. M.: Blood changes following gastrectomy in monkeys, *Proc. Soc. Exper. Biol. and Med.*, 1934, xxxii, 310-312.
- 12. GOODALL, J. R., and GOTTLIEB, R.: Association of pregnancy, hypochromic anemia and achlorhydria; preliminary report, *Can. Med. Assoc. Jr.*, 1936, xxxv, 50-53.
- 13. GOODMAN, L., GEIGER, A. J., and CLAIBORN, L. N.: Antianemia potency of liver after gastrectomy in swine, *Proc. Soc. Exper. Biol. and Med.*, 1935, xxxii, 810-812.
- 14. GREENSPON, E. A.: Nature of antipernicious anemia principle in stomach; method to improve stomach preparations, *Jr. Am. Med. Assoc.*, 1936, cvi, 266-271.
- 15. GROEN, J.: 1935, *Scheltema und Kolkema's Boekhandel*, Amsterdam.
- 16. GUTZEIT, K.: Schwere Anämien und Systemerkrankungen des Mesenchyms beim magenlosen Hund, *Verhandl. d. deutsch. Gesellsch. f. inn. Med.*, 1932, Kong. 44, 478-481.
- 17. HANES, F. M., HANSEN-PRÜSS, D. C., and EDWARDS, J. H.: Feeding of modified gastric juice in pernicious anemia, *Jr. Am. Med. Assoc.*, 1936, cvi, 2058-2059.

18. HELMER, O. M., FOUTS, P. J., and ZERFAS, L. G.: Relationship of intrinsic factor to hematopoietic material in concentrated human gastric juice, *Am. Jr. Med. Sci.*, 1934, clxxxviii, 184-193.
19. ISAACS, R., and STURGIS, C. C.: Some newer remedies in treatment of pernicious anemia; desiccated stomach, *Jr. Am. Med. Assoc.*, 1930, xcv, 585-587.
20. a. IVY, A. C., MORGAN, J. E., and FARRELL, J. I.: Effects of total gastrectomy; experimental achylia gastrica in dogs with occurrence of spontaneous anemia and anemia of pregnancy, *Surg., Gynec. and Obst.*, 1931, liii, 611-620.
 b. BURGESS, J. P., MORGAN, J. E., and IVY, A. C.: Effect of various stomach preparations in pernicious anemia, *Proc. Soc. Exper. Biol. and Med.*, 1931, xxviii, 371-372.
21. JUNG, F. T.: 36th Annual Report of Am. Gastroenterological Assoc., 1933.
22. KLEIN, L., and WILKINSON, J. F.: Investigations on nature of hemopoietin, antianemic substance in hog's stomach, *Biochem. Jr.*, 1934, xxviii, 1684.
23. MAGNUS, H. A., and UNGLEY, C. C.: Gastric lesions in pernicious anemia, *Lancet*, 1938, i, 420-421.
24. MAISON, G. L., and IVY, A. C.: Gastrectomy and subsequent hematologic studies in the hog, *Proc. Soc. Exper. Biol. and Med.*, 1934, xxxi, 554-556.
25. MANN, F. C.: Total gastrectomy: Report of a successful operation, *Proc. Staff Meet. Mayo Clin.*, 1929, iv, 293-295.
 MANN, F. C.: Gastrectomy; experimental study, *Ann. Surg.*, 1932, xcv, 455-463.
26. a. MEULENGRACHT, E.: Continued investigations on presence of antianemic factor in preparations of dried stomach substance from cardia, fundus, and pylorus, and duodenum; preparations from duodenum, *Acta med. Scandin.*, 1935, lxxxv, 79-88.
 b. MEULENGRACHT, E.: Continued investigations on presence of antianemic factor in preparations of dried stomach substance from cardia, fundus and pylorus regions; preparations from cardia region, *Acta med. Scandin.*, 1935, lxxxv, 50-78.
 c. MEULENGRACHT, E.: Glands of stomach in relation to pernicious anemia; with special reference to glands in pyloric region, *Proc. Roy. Soc. Med.*, 1935, xxviii, 841-870.
27. MORRIS, R. S., SCHIFF, L., FOULGER, J. H., RICH, M. L., and SHERMAN, J. E.: Treatment of pernicious anemia; effect of single injection of concentrated gastric juice (addisin), *Jr. Am. Med. Assoc.*, 1933, c, 171-173.
 MORRIS, R. S., SCHIFF, L., FOULGER, J. H., and RICH, M. L.: Further studies on addisin in diseases of blood, *Trans. Assoc. Am. Phys.*, 1933, xlviii, 298-304.
28. MCCOLLUM, E. V., and SIMONDS, N. J.: A study in the dietary essential, water-soluble B, in relation to its solubility and stability toward reagents, *Jr. Biol. Chem.*, 1918, xxxiii, 55.
29. a. PETRI, S., BØGGILD, D., OHLSEN, A. S., and BUSCH, F.: Experimentelle Untersuchungen über gastrogene Anämien (bei Hunden), *Acta path. et microbiol. Scandin.*, 1935, xii, 329-351.
 b. PETRI, S., BØGGILD, D., OHLSEN, A. S., and WANSCHER, O.: Untersuchungen über gastrogene Anämien und damit einhergehender Avitaminoseveränderungen; über die Schweinen nach Ventriklexirpation beobachteten Veränderungen, *Acta path. et microbiol. Scandin.*, 1937, xiv, 111-120.
30. MILLER, D. K., and RHOADS, C. P.: Experimental production of loss of hematopoietic elements of gastric secretion and of liver in swine with achlorhydria and anemia, *Jr. Clin. Invest.*, 1935, xiv, 153-172.
31. ROSAHN, P. D.: New capillary hematocrit, *Proc. Soc. Exper. Biol. and Med.*, 1931, xxviii, 491-492.
32. ROWLAND, V. C.: Pernicious or hemolytic anemia of pregnancy, *Jr. Am. Med. Assoc.*, 1924, lxxxii, 372-375.
33. SCHEMENSKY, W.: Zur Pathologie der perniziösen Anämie. Therapeutische Erfolge mit Verfütterung getrockneten Schweinedickdarpulvers. Mit einem Anhang: Therapeutische Betrachtungen zur Colitis gravis, *Ztschr. f. klin. Med.*, 1935, cxxviii, 428-438.

- SCHEMENSKY, W.: Zur Pathologie der perniziösen Anämie. Therapeutische Erfolge mit der Verfütterung getrockneten Schweinedickdarms, Deutsche med. Wchnschr., 1935, lxi, 961-962.
34. SHUMAKER, H. B., JR., and WINTROBE, M. M.: Experimental gastrectomy; effects on blood morphology, especially when complicated by infection or liver damage, Bull. Johns Hopkins Hosp., 1935, lvii, 384-402.
35. SHARP, E. A.: Antianemic factor in desiccated stomach, Jr. Am. Med. Assoc., 1929, xciii, 749.
36. SHARP, E. A., McKEAN, R. M., and VONDER HEIDE, E. C.: Pernicious anemia; behavior of various extracts of stomach and duodenum used to induce remissions, ANN. INT. MED., 1931, iv, 1282-1286.
37. SINGER, K.: Experimentelle Beiträge zum Problem der Pathogenese der perniziösen Anämie; zur Kenntnis der Anämien bei künstlich mit *Bothriocephalus latus* infizierten agastrischen Hunden sowie der Sekretionsverhältnisse des Castleschen Prinzips bei dieser Tierart, Ztschr. f. d. ges. exper. Med., 1935, xcv, 762-771.
38. STRAUSS, M. B., and CASTLE, W. B.: Studies of anemia in pregnancy; gastric secretion in pregnancy and puerperium, Am. Jr. Med. Sci., 1932, clxxxiv, 655-662.
- STRAUSS, M. B., and CASTLE, W. B.: Studies of anemia in pregnancy; relationship of dietary deficiency and gastric secretion to blood formation during pregnancy, Am. Jr. Med. Sci., 1932, clxxxiv, 663-673.
- STRAUSS, M. B., and CASTLE, W. B.: Studies of anemia in pregnancy; etiologic relationship of gastric secretory defects and dietary deficiency to hypochromic and macrocytic (pernicious) anemias of pregnancy and treatment of these conditions, Am. Jr. Med. Sci., 1933, clxxxv, 539-551.
- STRAUSS, M. B.: Etiology and treatment of anemia in pregnancy, Jr. Am. Med. Assoc., 1934, cii, 281-283.
- STRAUSS, M. B.: Etiology and prevention of anemia in pregnancy, ANN. INT. MED., 1935, ix, 38-41.
39. a. STURGIS, C. C., and ISAACS, R.: Desiccated stomach in treatment of pernicious anemia, Jr. Am. Med. Assoc., 1929, xciii, 747-749.
- b. STURGIS, C. C., and ISAACS, R.: Clinical and experimental observations on the treatment of pernicious anemia with desiccated stomach and with liver extract, ANN. INT. MED., 1931, v, 131-158.
40. UNGLEY, C. C.: Observations on Castle's intrinsic factor in pernicious anemia, Lancet, 1936, i, 1232-1235.
41. WILKINSON, J. F.: Hemopoietic hormone in pernicious anemia, Brit. Med. Jr., 1932, ii, 1163.
42. a. WILLS, L., and BILLMORIA, H. S.: Studies in pernicious anemia in pregnancy; production of macrocytic anemia in monkeys by deficient feeding, Indian. Jr. Med. Res., 1932, xx, 391-402.
- b. WILLS, L., and STEWART, A.: Experimental anemia in monkeys, with special reference to macrocytic anemia, Brit. Jr. Exper. Path., 1935, xvi, 444-453.
- c. WILLS, L., CLUTTERBUCK, P. W., and EVANS, B. D. F.: A new factor in the production and cure of certain macrocytic anemias, Lancet, 1937, i, 311-314.
43. VLADOS, H., BAGDASAROV, A., DULCIN, M., and BONDARENKO, E.: Part taken by stomach in regulation of blood formation, Acta med. Scand., 1936, lxxxviii, 295-311.

THE USE OF SULFANILAMIDE IN PULMONARY TUBERCULOSIS; PRELIMINARY REPORT *

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THE chemotherapeutic effects of sulfanilamide (para-amino-benzene sulfonamide) in certain infectious diseases have been successfully demonstrated in humans and in experimental animals. Although the best results have been obtained in beta hemolytic streptococcic infections, it has been used in other conditions, as gonococcic urethritis, meningococcus meningitis, colon bacillus pyelitis, brucellosis, etc., with varying degrees of success. Intensive studies have been carried out by Long and Bliss, who in a recent article¹ give an excellent bibliography of investigations in this field.

However, the possible use of sulfanilamide in chronic granulomatous infections has so far received little if any attention. In January 1938, Rich and Follis, Jr.² reported their investigations with sulfanilamide in experimental tuberculosis. Of 59 guinea pigs inoculated with virulent tubercle bacilli, 31 were treated with orally administered crystalline sulfanilamide and 28 were used as controls. After five to six weeks the controls showed large local lesions and regional nodes, greatly enlarged tracheobronchial glands and enlarged spleens, whereas in the treated animals the lesions were minute and there was no splenomegaly. Microscopically, tubercles were found in all the treated animals, but to a much less extent than in the controls. Whether this difference was caused by inhibition of bacillary growth by the sulfanilamide or not could not be determined. Although sulfanilamide was apparently of value in animal tuberculosis, no conclusions could be drawn concerning its chemotherapeutic effect in humans. In September 1938, Dietrich³ reported his investigations along similar experimental lines and found that relatively large doses of prontosil failed to eliminate the tubercle bacilli or halt their spread in infected guinea pigs. Actually, the untreated (control) animals lived much longer than the treated ones.

Because of this controversial experimental background, and because we were desirous of determining what sulfanilamide could do in a chronic disease, we decided to use this drug in clinical pulmonary tuberculosis. Thirty-five patients, 20 males and 15 females, with pulmonary tuberculosis of the moderately and far-advanced types, were treated with sulfanilamide over a period of from 10 to 15 weeks. The drug was administered orally in 10 grain doses three times daily, with equivalent amounts of sodium bicarbonate. This was gradually increased to 20 grains three times daily over a period of one month and for the following six to 10 weeks each patient re-

* Received for publication November 7, 1938.

From the Tuberculosis Division, Cook County Hospital, Chicago.

ceived this maximum dose daily.* No other medication was given, and magnesium sulphate, salicylates and undue exposure to sunlight were carefully avoided.

Weights were checked at intervals; temperature, pulse and respiration were recorded daily; sputum was examined bimonthly; reactions and evidence of toxicity were carefully noted; complete blood counts were made; and each patient was roentgenographically studied. None received artificial pneumothorax, and all were either semiambulant or confined to bed, and were subjected to the standard therapeutic regimen of the hospital. For controls, records of each patient prior to and after the experiment, as well as the findings in a similar group of patients treated with pneumothorax, were used.

RESULTS

Other than an initial psychic stimulus because something new was being used, the sulfanilamide did not appear to cause any physical or subjective improvement in any of the patients. Extrapulmonary tuberculous complications were present in 14 patients (three had bone involvement, six laryngitis, two enteritis, one epididymitis and two suppurating cervical glands), and in none was there noted any therapeutic effect from the sulfanilamide.

Toxic side-effects were plentiful. Nine patients complained of severe and continued headache after having received the drug consistently for three weeks. Stopping the sulfanilamide caused the headaches to disappear, but they recurred when the drug was readministered. That this reaction was not of psychogenic origin was indicated by the fact that substituting lactose tablets of the same size, shape and color as the sulfanilamide tablets failed to cause recurrence of the headaches. Cyanosis was common but was of no great significance. Blood spectroscopic examinations for met- and sulf-hemoglobin were not done. Severe toxic effects, as severe anemias, granulocytopenia, etc., were not evident although 20 patients were markedly anemic before sulfanilamide was administered.

DISCUSSION

To our knowledge no previous clinical study of this type has been previously reported. Our results or lack of results was not unexpected, and is compatible with our knowledge of the pathology of tuberculosis. In the acute diseases the offending microorganisms can be readily reached by blood and lymph-borne drugs. In tuberculosis, however, the tubercle bacilli are isolated in relatively avascular lesions which are walled off by fibroblasts and epithelioid cells, so that the central portions undergo an avascular necrosis (caseation). This provides an almost impregnable barrier to intracellular fluids. Thus, Rich and Follis, Jr., found living tubercle bacilli in their animals in spite of treatment with sulfanilamide and, although Dietrich first

* Sulfanilamide was made available by Upjohn Co., Kalamazoo, Michigan.

saturated some animals with sulfanilamide before inoculating with tubercle bacilli, the course of the disease was not affected. Likewise, in our patients not one of the sputum positive cases was rendered sputum negative. It is apparent, therefore, that even if sulfanilamide killed tubercle bacilli in vitro, which has not been experimentally established, there is no theoretical basis for hoping for a similarly favorable result in vivo.

That sulfanilamide is of no value whatsoever in pulmonary tuberculosis cannot be concluded from this clinical experiment for two reasons. First, blood cultures for tubercle bacillemiá were not done, and it is possible that in the presence of such positive cultures this drug may be of therapeutic value. Bliss and Long⁴ found that sulfanilamide acts in vivo by bringing about a change in susceptible microorganisms which permits phagocytosis; and Osgood and Brownlee⁵ found in their in vitro experiments that the major action of sulfanilamide on beta hemolytic streptococci was that of neutralization of the toxins without any phagocytic effect. Secondly, not infrequently streptococci are present in tuberculosis as associated or secondary invaders, so that sulfanilamide may be of value.

Although relatively few toxic effects from the sulfanilamide were observed in spite of its prolonged administration, it must be constantly remembered that this drug is capable of serious toxic reactions, particularly in susceptible persons. Caution is, therefore, necessary.

CONCLUSIONS

Orally administered sulfanilamide is of no apparent value in altering the course in patients with pulmonary tuberculosis. The questions of the value of sulfanilamide in pulmonary tuberculosis associated with tubercle bacillemia and/or with secondary streptococcic infection are being investigated.

BIBLIOGRAPHY

1. LONG, P. H., and BLISS, ELEANOR A.: Clinical use of sulfanilamide and its derivatives in the treatment of infectious diseases, *ANN. INT. MED.*, 1937, xi, 575.
2. RICH, ARNOLD R., and FOLLIS, RICHARD H., JR.: Inhibitory effect of sulfanilamide on the development of experimental tuberculosis in the guinea pig, *Bull. Johns Hopkins Hosp.*, 1938, lxii, 77.
3. DIETRICH, HARRY F.: Prontosil in experimental tuberculosis, *Am. Rev. Tuberc.*, 1938, xxxviii, 388.
4. BLISS, ELEANOR A., and LONG, P. H.: Observations on the mode of action of sulfanilamide, *Jr. Am. Med. Assoc.*, 1937, cix, 1524.
5. OSGOOD, E. E., and BROWNLEE, INEZ E.: Culture of human marrow: Studies on the mode of action of sulfanilamide, *Jr. Am. Med. Assoc.*, 1938, cx, 349.

Since the acceptance of this article, the following papers dealing with the subject have appeared:

- SMITHBURN, K. C.: Inefficiency of prontosil in experimental tuberculosis, *Proc. Soc. Exper. Biol. and Med.*, 1938, xxxviii, 574-575.
- GREEY, P. H., CAMPBELL, H. H., and COLLY, A. W.: Effect of sulfanilamide on experimental tuberculosis in the guinea pig, *Proc. Soc. Exper. Biol. and Med.*, 1938, xxxix, 22-24.

- BUTTLE, G. A. H., and PARISH, H. J.: Treatment of tuberculosis in guinea pigs with sulfanilamide, *Brit. Med. Jr.*, 1938, ii, 776-777.
- GREEY, P. H., BODDINGTON, G. D. H., and LITTLE, M. H.: Sulfanilamide and related compounds in experimental tuberculosis, *Proc. Soc. Exper. Biol. and Med.*, 1939, xl, 418-420.
- FANIEL, H., JEURISSEN, A., COURTOIS, R., and DWELSHAUVERS, F.: Sulfanilamide and tuberculosis, *Bruxelles-méd.*, 1939, xix, 725.
- CLIMENKO, D. R., and SCHMIDT, R. L.: N'-Dodecanoylsulfanilamide. II. Experimental infections with beta hemolytic streptococci and human tubercle bacilli, *Pathological Laboratory, Calco Chemical Co., Cold Spring Harbor, May, 1939.* (Personal communication.)

GENERALIZED CAPILLARY AND ARTERIOLAR THROMBOSIS

REPORT OF TWO CASES WITH A DISCUSSION OF THE LITERATURE*

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THESE two cases are being reported together because they show similar pathologic changes even though clinically they differ entirely. The pathologic process is characterized by generalized arteriolar and capillary thrombosis.

While we realize that atypical verrucous endocarditis with a skin lesion resembling lupus erythematosus was described by Libman and Sacks¹ in 1923, and that Moschcowitz² the following year presented a case before the N. Y. Pathological Society under the title of "Hyaline Thrombosis of the Terminal Arterioles and Capillaries (A Hitherto Undescribed Disease)," we feel that despite the fact of the description of these two widely differing clinical conditions, the identical pathological lesions which were found may make them the same disease; a disease essentially of the blood vessels and in particular of the smaller branches of the arterial system. Besides this the arterial lesions here described may possibly belong in the same category as periarteritis nodosa and may represent a variant of this disease.

CASE REPORTS

CASE OF PURPURA WITH CAPILLARY THROMBI†

Case 1. H. K., female, aged 18, single. Admitted to Lebanon Hospital, service of Dr. C. Goldmark, April 25, 1932, and died May 13, 1932. Two years before admission and lasting for one year the patient suffered with vague joint pains. After this she had an occasional sore throat and a mild gripe. Aside from this, she was well until about three months ago when she was confined to bed with what was called influenza. This cleared up except for persisting stiffness and numbness of the body which also included the face. A few days later, the influenza-like symptoms recurred. One week before her admission her temperature rose to 103° F. This was accompanied by coryza, sore throat, generalized pains over the body, and cough productive of green expectoration. In the week before admission she also vomited occasionally. She had some polyuria and a nocturia of two to three times. The urine was described as dark brown.

Her last menstrual period was nine days before admission. Her menstrual history in general was negative.

On *physical examination* the patient looked quite pale and uncomfortable. There were a number of discolorations over the entire body, looking like hemorrhagic nevi. Besides this there were a number of petechia-like lesions over the skin, the mucous

* Received for publication February 21, 1938.

† Case presented at meeting of Alumni of Lebanon Hospital.

membranes and in the retinae. She had a subicteric tint to the sclerae and skin. There was an old herpes labialis. The posterior chain of cervical glands was palpable on both sides. The lungs were negative. The heart sounds were muffled, but no murmurs were heard. There were several dropped beats per minute. The liver was felt two fingers-breadth below the free costal margin. The spleen was not felt. Later a faint systolic murmur was heard at the heart apex. This was not transmitted. There was percussion tenderness over the sternum and tibiae, together with tenderness of the muscles of the thigh.

Two days after admission the hemorrhagic spots, particularly those on the face, showed a tendency to bleed. The crusted lesions (herpes) on the upper lip also bled.



FIG. 1. Case 1. Heart showing several thrombosed vessels.

Spleen and liver were now definitely enlarged. A blowing systolic murmur was now heard over the entire heart.

Examination of the fundus oculi showed numerous hemorrhages.

On the last day of her life, the patient developed a right hemiplegia with a positive Babinski sign on the right. She became comatose. The retinae showed profuse hemorrhages extending over the discs.

LABORATORY FINDINGS. *Urines.* Specific gravity 1.002–1.020. Red and white blood cells and various kinds of casts were constantly present. Bence-Jones protein (proteose) was not found but albumin was present. Urobilinogen was present at times, but in other specimens was absent.

Blood Cultures. Two were sterile.

Blood Chemistry. Non-protein nitrogen 32 mg. per cent; sugar 109 mg.; urea nitrogen 16 mg.; uric acid 2.7 mg.; total cholesterol 139 mg.; free cholesterol 103 mg.; cholesterol ester 36 mg.; calcium 9.1 mg.; phosphorus 3.7 mg. Van den Bergh 0.6; icterus index 14.2; bilirubin dilution 1–110. Carbon dioxide combining power 56 volumes per cent.

Stools. Strongly positive for blood. No ova or parasites found.

Blood Counts. Hemoglobin 25-46 per cent; red blood cells 1,400,000-2,000,000; white blood cells 3,000-14,000. Polymorphonuclears 86 to 78 per cent; staff forms 50 to 74 per cent. Normoblasts were very numerous. Reticulocytes 31 to 80 per cent. Platelets 50,000-100,000. *Bleeding time.* Two to four minutes. *Coagulation time.* Five minutes. Clot non-retractile in 24 hours. *Fragility of red blood cells.* Hemolysis began at salt concentration of 0.44 and was complete at 0.28 per cent. *Tourniquet test.* Negative. *Wassermann test.* Negative. *Blood Pressures.* Systolic 100 to 110; diastolic 50 to 70. *Pulse Rate.* 90 to 100; respiratory rate 24; temperature irregular 101°-104° F. during first week, then 100° F. Prelethal rise to 103°.

COMMENT

The clinical diagnosis in this case at various times ranged between aplastic anemia, hemolytic icterus, purpura hemorrhagica and bacterial endocarditis.

In analyzing this case, we see the rapid development of a hemorrhagic tendency, in the sense of a purpura with hemorrhages over the skin, mucous membranes, in the retinae and possibly also in the brain. This was accompanied by a subicteric tint to the skin and sclerae, and by the laboratory evidences of icterus.

The course was febrile. The blood showed a thrombocytopenia, a severe secondary anemia, usually leukopenia with a high staff cell count, a very high reticulocyte count and numerous normoblasts.

The diagnosis of aplastic anemia had to be abandoned because of the finding of many young cells, viz., reticulocytes, staff cells and normoblasts indicating not aplasia but rather active hemopoiesis in the bone marrow.

The diagnosis of familial hemolytic icterus was untenable because of the negative family history, but that of the acquired form was very plausible in view of the large number of reticulocytes. The resistance of the red blood cells to hypotonic salt solutions was, however, increased. Studies for spherocytosis were not done. The spleen was not particularly hard and the tendency to skin and mucosal hemorrhages was too great to accord with this diagnosis.

Purpura hemorrhagica or thrombocytopenic purpura was present as shown by the low platelet count, the purpuric lesions, the gastrointestinal bleeding, and the non-retractile clot. It did not seem, however, that the disease was an essential purpura. It seemed rather that the thrombocytopenia was a secondary manifestation. This contention was proved at the post-mortem examination.

POSTMORTEM EXAMINATION (DR. J. C. EHRLICH)

General Appearance. The body is that of a white, well developed but poorly nourished girl, aged 18. The skin is quite pallid, with a yellowish tinge. Recent incisions, each two inches in length, are present in both antecubital spaces. Many small petechiae are scattered over the body. Superficial lymph nodes are not palpable. There is no edema present. There is a moderate amount of postmortem lividity over the back.

Incision. (Y-Incision.) The incision is made from both axillary spaces to the epigastrium, and mid-abdominal to the symphysis. All viscera are removed, an incision from the symphysis to the left knee is also made, and the left femur is removed.

Peritoneal Cavity. The viscera are in normal situ. There are no evidences of exudate, adhesions or excess fluid in the peritoneal cavity. No anomalies are evident.

Thoracic Cavity. There are no excess fluid, exudate or adhesions present. The organs are in normal situ. The thoracic surface of the diaphragm on each side is studded with many petechiae.

Pericardium. The pericardial cavity contains about 100 c.c. of straw-colored, thin serous fluid, but no exudate or adhesions. The visceral pericardium, and particularly that covering the right auricle, is studded with innumerable petechiae.

Heart and Great Vessels. The heart weighs 320 grams and is normal in size and shape. It is contracted and brownish red in color. The pericardial fat tissue is not increased. The myocardium is everywhere firm, without areas of softening. Beneath the pericardium and on section, tiny pale, punctate scars can be seen in the myocardium. The right auricle is normal in size and shape, and possesses normal vascular communications with the superior and inferior vena cavae and the coronary sinus. The endocardium is smooth, thin and glistening. The auricular appendage is not thrombosed. The tricuspid valvular ring is slightly distended. The tricuspid valves are thin and shiny with normal attachments of the chordae tendineae. There is no evidence of old or recent endocarditis. The right ventricle is slightly dilated, and the muscular wall is of normal thickness. The ventricular endocardium is smooth. There are no thrombi present, but occasional petechiae are seen. The pulmonary valves are thin, normal in structure, and free of endocarditis. The pulmonary artery is of normal size and the intima does not show any evidence of atherosclerotic changes. The left auricle is normal in size, and is lined by a smooth, thin, glistening endocardium. The left auricular appendage is not thrombosed. The mitral valve is entirely normal in appearance and shows slight tension thickening of the aortic cusp. There is no evidence of old or recent endocarditis. The endocardium of the left ventricle appears normal, except for a few petechial hemorrhages. The musculature of the left ventricle is of normal thickness, color and consistency. The aortic cusps are normal, except for slight tension changes. The coronary orifices are in their normal locations and widely patent. The aorta itself is not widened, maintains full elasticity, and possesses a smooth intima which is studded with occasional yellowish atherosclerotic plaques. The superior and inferior vena cavae appear normal, as do also the large branches of the aorta.

Lungs. The lungs together weigh 775 grams. They are very pale. The pleura is smooth and the lungs appear adequately aerated. They are somewhat heavier than normal to the touch, and on section reveal a moderate amount of edema. There are no evidences of pneumonic involvement or of infarcts. The trachea and bronchi contain some frothy reddish brown fluid. The mucosa of the tracheo-bronchial tree is smooth and glistening and moderately congested.

Gastrointestinal Tract. The esophagus is normal in appearance. The mucosa of the stomach is studded with innumerable petechiae. The small intestine and its mesentery appear normal, except at a point about two feet proximal to the ileo-cecal valve, where there is a small Meckel's diverticulum measuring $1\frac{1}{2}$ " in length. The mucosa of the large intestine shows distinct melanosis, and is dark brownish black in color, with a fine silvery gray network. The mucosa of the large bowel contains numerous petechiae.

Liver. The liver weighs 1425 grams. The edge of the liver reaches two inches below the inferior costal border. The capsule of the liver is smooth, glistening and translucent, and is pale brown in color. The lobulation and consistency of the liver are normal. Cut section shows only moderate congestion, and is similar in color to

the surface. The gall-bladder and bile passageways, both intra- and extra-hepatic, do not show any abnormalities.

Pancreas. The pancreas is normal in size, shape and consistency. The parenchyma does not contain an unusual amount of fat. The pancreatic ducts do not show any abnormalities. The splenic vein and artery are not unusual.

Spleen. The spleen shows a diffuse uniform enlargement to about twice the normal size. It weighs 275 grams. Its capsule is smooth, dark reddish gray in color, and fairly dense. The consistency of the spleen is slightly softer than normal. Cut surface has the appearance of chronic passive congestion. The Malpighian follicles stand out distinctly. The pulp cannot be scraped out easily.

Adrenals. The adrenal glands are in their normal situ. The right adrenal vein is occluded and thrombosed, and there is a small hemorrhage into the peri-nephritic tissue on that side. On section, the cortex of the adrenal glands is of normal thickness and bright yellow in color. There is very little autolysis.

Genito-Urinary System. Kidneys. The left kidney weighs 150 grams, the right kidney weighs 180 grams. The capsules can be stripped easily, revealing a smooth, shiny, dark brown surface, with many small petechial hemorrhages and a few larger hemorrhages; some of them reaching $1\frac{1}{2}$ cm. in diameter. There are two small infarcts in the right kidney, each of which produces a sharply outlined depression on the surface of the kidney. Cut section is dark brown in color, and there are many conspicuous minute hemorrhages. Normal renal markings are present and distinct. The pelvis of the right kidney is filled with blood. The ureters and bladder do not show any abnormalities.

Genital Organs. The uterus is infantile in size, but otherwise normal. The cervix appears markedly congested.

Lymph Nodes. Moderate hyperplasia is present of the axillary, mesenteric, and para-aortic glands.

Bones. The marrow of the sternum is dark red and has a thick creamy consistency when expressed. The vertebral marrow appears normal, save for fibrous streaks which occasionally cross irregularly through it. The left femur on section reveals a conspicuous red marrow, soft and creamy when expressed, throughout the entire length of the bone, including epiphysis and shaft.

MICROSCOPIC FINDINGS

Heart. The auricular endocardium, valve ring and valve are normal. Numerous small blood vessels are thrombosed. These thrombi appear in the smaller arterioles and capillaries, and perhaps also in the venules. The thrombi have a pink, homogeneous and slightly fibrillar appearance, which in many instances show endothelial reaction. The endothelial cells may cover the thrombus or endothelial cells may be included within the thrombus. Some of these thrombi are adherent to the vessel wall. Others appear to lie within the lumen of the vessel. The myocardium shows very little fibrosis, which would appear to indicate that these vascular occlusions are either incomplete or of very recent origin. Elastica stains indicate that many of the occluded vessels are of arterial nature. One cannot exclude also venules. In the main these thrombi have a clear hyaline appearance.

Lungs. There is diffuse edema. Intense capillary congestion is present. Many capillaries appear to be tightly packed with red blood cells. Thrombi as seen in other organs are not clearly made out in the lung. However, several pulmonary vessels present marked intimal thickenings, almost to the point of occlusion, and one vessel is found with complete hyaline thrombosis.

Liver. The parenchyma of the liver and the capsule appear normal. Several hepatic arterioles show hyaline thrombi similar to those found elsewhere in the body. Bile canaliculae and bile ducts do not show any abnormalities.

Spleen. There is intense active congestion of the spleen with filling of the pulp with erythrocytes, while the sinuses remain relatively empty. Splenic follicles are very distinctly outlined. Several large trabecular veins show complete occlusion by hyaline thrombi. The cellular picture of the pulp is quite normal.

Kidney. There is an enormous amount of hemosiderin in the tubular epithelium. Numerous hyaline thrombi are seen throughout the kidney. Occasional hyaline thrombi are found in the efferent arterioles and in the glomerular loops. There are several areas of focal cortical atrophy, representing early anemic infarcts.

Pancreas. The capillaries and small blood vessels contain numerous hyaline thrombi.

Thymus. Many calcified Hassall's corpuscles are present. There are no vascular thrombi.

Lymph Nodes. The lymph nodes reveal sinus endothelial hyperplasia.

Adrenals. There are no changes in the adrenal.

Cerebrum. There is a petechial hemorrhage in the pia. There are no thromboses.

Skin. No hemorrhages are found.

ANATOMICAL DIAGNOSIS

1. *Cause of Death:* Anemia. Multiple vascular thromboses.
2. Anemia of unknown origin.
3. Generalized thromboses of small blood vessels.
4. Petechiae in skin, diaphragm, pericardium, endocardium, gastrointestinal tract.
5. Hyperplasia of bone marrow.
6. Pulmonary edema.
7. Meckel's diverticulum.
8. Melanosis of ascending and transverse colon.
9. Thrombosis of left adrenal vein.
10. Infarcts of kidney.
11. Hemosiderosis of kidneys.
12. Hemorrhage into right kidney pelvis.
13. Hyperplasia of axillary, mesenteric and para-aortic glands.

CASE OF ATYPICAL VERRUCOUS ENDOCARDITIS WITH LUPUS ERYTHEMATOSUS

Case 2. C. L., female, aged 27, single. Admitted to Lebanon Hospital, service of Dr. Carl Goldmark, June 14, 1932, and died June 20, 1932. This patient was first seen by Dr. Lossow on June 3, 1931, with swelling and stiffness of some of the small joints of her right hand. These joints became swollen on use and subsided with rest. There was no fever. A roentgenogram of the chest showed that the lungs were normal but heart showed a mitral contour. She was carefully examined for foci of infection but none was found. At the end of June 1931 she had an axillary adenitis. In July of the same year an infected sebaceous cyst was removed from her right axilla. The arthritic pain persisted until August. Early in September she became exhausted. A blood count done at this time showed: hemoglobin 68 per cent; red blood cells 4,600,000; white blood cells 6000; polymorphonuclears 69 per cent, lymphocytes 25 per cent, mononuclears 3 per cent, myelocytes 3 per cent. A slight shift to the left was indicated. One of us (S. G.) saw her on October 23, 1931, and found her to be suffering with a moderate degree of cardiac decompensation. Her previous history taken at this time was negative with the exception of diphtheria at the age of 10. There was no family history of tuberculosis.

Physical examination on October 23, 1931, revealed a diastolic murmur at the heart apex and along the left border of the sternum, together with a suggestive pericardial friction rub. There was some edema of the legs. The liver was felt one

finger-breadth below the costal margin. Retinal examination revealed choroidal pigmentation. No skin lesions were present. Bed rest and salicylates were prescribed. *Diagnosis* at this time was rheumatic fever with pancarditis, mitral stenosis and pericarditis.

Eight months later her left ankle became painful and swollen and she began to have fever. Together with this she developed a cough which persisted for two weeks.

A butterfly skin lesion was noted over both malar prominences, the nose and part of the forehead. This was rough, red, somewhat indurated and scaly. Similar lesions were present on the upper part of the chest and over both shins and arms. The patient stated that these lesions were the result of sunburn from purposeful exposure. She had clubbed fingers. The mucous membranes showed no abnormalities.

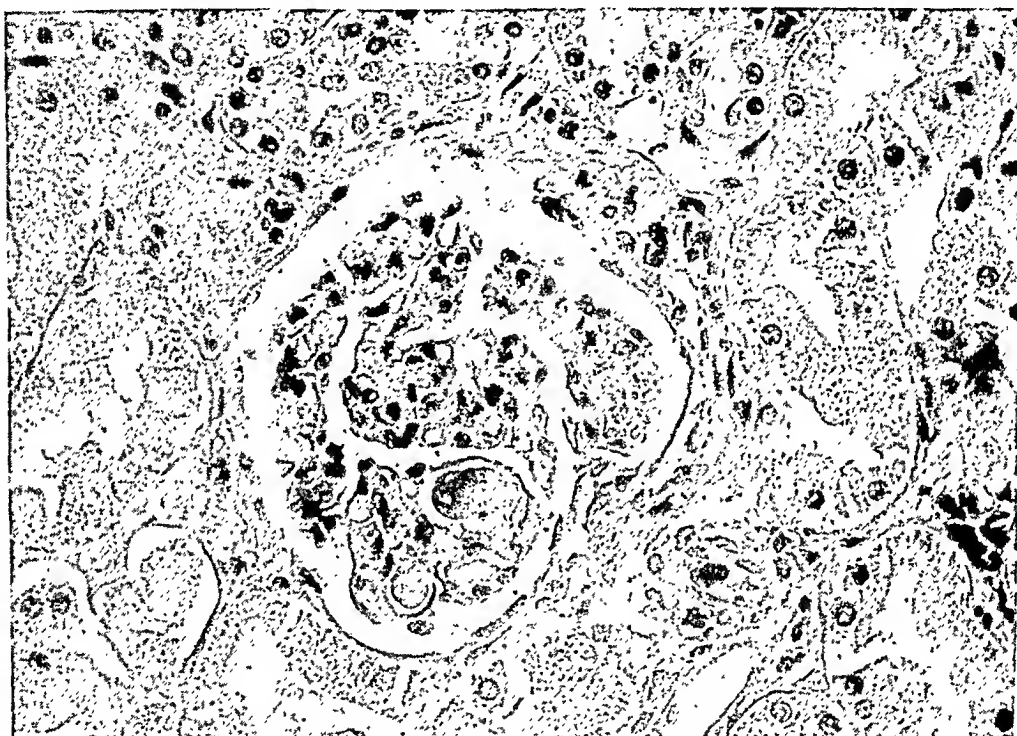


FIG. 2. Case 2. Glomerulus containing hyaline thrombi in several capillary loops.

There was dullness at both lung bases, more at the left, with numerous crepitant and subcrepitant râles and diminished breathing and fremitus—evidently bronchopneumonia.

The heart was enlarged both to right and left. A presystolic thrill followed by a sharp thud was felt over the precordium. At the apex a presystolic roughening was heard ending in a sharp first sound. At the fourth intercostal space to the left of the sternum a soft, blowing, diastolic murmur was heard. The second pulmonic sound was accentuated. A suggestive pericardial friction sound was heard over the base, particularly over the pulmonic area.

Liver and spleen were not felt. There was no Murphy sign. The eye grounds were negative except for the choroiditis previously noted (high myopia).

Clinical diagnosis at this time was rheumatic pancarditis with pericarditis and possible effusion, mitral stenosis and insufficiency, lupus erythematosus with accompanying cardiac lesion, bronchopneumonia and acute glomerulo-nephritis.

Two days after admission a petechial spot was found in the conjunctiva of the left lower lid.

Dermatological consultation was had with Dr. L. Chargin whose opinion was:

(1) A more or less generalized sunburn after exposure.

(2) Face and upper chest showed an erythematous eruption of the type associated with so-called acute lupus erythematosus. This type is not infrequently precipitated by sunburn. Whether this was in fact a true acute lupus erythematosus, the course would determine. This type is sometimes seen in subacute bacterial endocarditis and is an independent disease (possibly on a tuberculous basis according to some).

The patient developed oliguria almost to the extent of anuria, an increasing nitrogen retention, and finally died in uremia.

LABORATORY FINDINGS. *Roentgenogram, June 15, 1932.* Heart moderately enlarged to left. Mitral configuration. Lungs: Bronchopneumonic infiltrations of both bases. Thickened pleura right apex. Small interlobar effusion.

Urine. Albuminuria, high specific gravity, many hyaline and granular casts, white and red blood cells.

Blood. Moderate to severe anemia with hemoglobin 33-52 per cent. Red blood cells 3,800,000 to 3,150,000 and white blood cells 7000-10,000, normal differential with many young forms.

Blood Culture. Sterile once, and once showed an anhemolytic streptococcus later shown to be a contamination.

Blood Chemistry. The non-protein nitrogen rose from 26 to 108 mg. per cent, the latter with a creatinine of 8.6 mg. per cent.

Wassermann Test. This was positive twice.

Sputum. Negative for tubercle bacilli.

Temperature. 103°-105° F., with prelethal rise to 107° F.

Blood Pressure. Systolic 120 to 130; diastolic 80.

Pulse. Rapid.

COMMENT

The final clinical diagnosis in this case was atypical verrucous endocarditis with lupus erythematosus acutus disseminatus, rheumatic pancarditis, mitral stenosis and insufficiency, pericarditis, bronchopneumonia, acute glomerulonephritis, uremia.

Concerning the positive Wassermann tests it may be said that the condition was never clinically considered to be luetic, the heart condition in particular being considered either purely rheumatic or rheumatic with associated subacute bacterial endocarditis. In the literature Davis and Ayonen³ describe a similar case. They think that the positive Wassermann test is due to a disturbed colloid and lipid balance of the blood serum and not to the presence of syphilis.

POSTMORTEM EXAMINATION (DR. J. C. EHRLICH)

General Appearance. The body is that of a white adult female, aged 27, well developed, with proptosis of both eyes. There is an erythematous rash over both cheeks, extending to the nose, with crustaceous papules on the cheeks and upper and lower lips. Over both tibiae anteriorly, an erythematous rash is present (sunburn). There is no edema, petechiae, ecchymoses or jaundice present.

Incision. Incision was made from the manubrium to the symphysis pubis.

Abdomen. There is no free fluid or exudate, nor are there any adhesions or evidences of peritonitis. The intestines have a normal, smooth, glistening surface. The organs are in their normal situ.

Thorax. The diaphragm reaches the fifth intercostal space on the right and the sixth intercostal space on the left. There are multiple, easily broken fresh adhesions between the viscera and pleura on each side, with obliteration of the right costophrenic sinus by adhesions. There is no free fluid present in either chest.

Heart and Pericardium. The pericardial cavity contains about 75 c.c. of clear, straw-colored fluid. There is an area of fairly dense adhesions between the viscera and parietal pericardium near the apex anteriorly. The remainder of the pericardial surfaces appear smooth and glistening. The heart is normal in shape, and shows a moderate diffuse enlargement. It weighs 390 grams. The right auricle is slightly distended. The endocardium is smooth, and there are no abnormalities present in the superior or inferior vena cavae. The tricuspid valve ring is normal in circumference. The cusps are thin and free of vegetations. Their attachments to the chordae tendineae appear normal. The right ventricle is slightly distended. Its muscular wall is of normal thickness and there is no increase in epicardial fat. The pulmonary valves appear normal, as do the main branches of the pulmonary artery. The left auricle appears normal in size. Its endocardium is slightly thickened, but smooth. There are no thrombi in the auricle or in the left auricular appendage. The mitral valve shows a moderate degree of stenosis. The mitral cusps are fused at the commissure and they are diffusely thickened and contain some small plaques of calcium. The free edges of the mitral valve cusps are thickened and rolled over, pulling the insertions of the chordae tendineae to the under or ventricular surface of the valves. A fairly recent, soft, friable thrombotic endocarditis is present, which does not reveal any organisms on smear or culture. The left ventricle shows a moderate, diffuse hypertrophy, and is elongated somewhat from base to apex. The ventricular endocardium is smooth. Near the base there are several glistening white, stellate, small depressed scars in the muscle of the ventricle. The aortic cusps are also fused at the commissure and one of them shows a few small thrombotic vegetations. The mouths of the coronary arteries are patent and normal in appearance. The coronary arteries themselves show only slight sclerosis. The aorta retains normal elasticity and is lined by a smooth intima containing a few small atheromatous depressions. There is no evidence of lues.

Lungs. The lungs are normal in size. They are increased in consistency, very firm, and the left lung feels consolidated in the upper and lower lobes. The lobulation of the lungs is normal. The pleura is covered by a thick recent adherent fibrinous exudate, and on section the appearance is that of a confluent lobular pneumonia, involving upper and lower lobes. The pneumonia appears mainly to be in the gray stage. Cut surface is dry, granular and consolidated, and is the seat of a diffuse pneumonic infiltration. Distribution of the tracheal subdivisions is normal. The tracheo-bronchial mucosa is deeply congested. The trachea contains some blood-stained frothy fluid. Those branches of the pulmonary artery which can be dissected, appear normal.

Liver. The liver is normal in size and weighs 980 grams. Its capsule is smooth everywhere, except on the upper surface, where some small plaques of fibrinous exudate as a result of trans-diaphragmatic extension from the lungs, are present. The consistency of the liver is normal. The color of the surface on cut section is pale reddish brown, and the liver appears to contain a considerable amount of fat. The gallbladder and the intra- and extra-hepatic bile ducts do not show any abnormalities.

Spleen. The spleen is enlarged to about one and one-half times the normal size and weighs 190 grams. The capsule of the spleen shows a few flakes of fibrin, but is otherwise normal. The consistency of the spleen is fairly firm. On section, the pulp has a reddish gray appearance, with conspicuous follicles and trabeculae. The pulp can be scraped easily with a knife. There are no infarcts present.

Kidneys. The kidneys are normal in size and weigh together 220 grams. The capsules can be stripped easily, revealing a fairly smooth surface in which there are multiple depressed, irregular, reddish scars. These depressions are very shallow, dark

red in color, and sharply demarcated from the surrounding raised and more normal looking parenchyma. The appearance of these scars, many of which are confluent, producing channel-like depressions, is characteristic of the renal changes in atypical verrucous endocarditis. On cross section, similar scarred areas can be seen. Otherwise the cortical medullary markings appear quite normal. The pelvis, calyces, ureters and bladder are negative.

Genital Organs. The uterus is slightly enlarged, due to the presence of a few small fibromyomata. It appears otherwise negative. The tubes are slightly thickened, and the ovaries are slightly enlarged with thickened capsules. The surface is congested and suggests chronic oöphoritis. The ovaries contain a few small follicular cysts.

MICROSCOPIC FINDINGS

Heart. Section of the mitral valve reveals marked diffuse fibrosis and thickening. The valve is vascularized and contains proliferated young fibroblasts and a few round cells. Blood vessels in the valve are injected. On the surface of the valve near the closing margin, there is a large thrombo-endocarditis. The thrombus is incorporated in the superficial part of the valve, and is partly covered by endothelium. The thrombus does not contain any inflammatory cells or bacteria. The chordae tendineae are also markedly thickened. The ring of the valve contains a few round cells, but does not appear vascularized in the section examined. The auricular endocardium shows some irregular thickening. The myocardium of the ventricle and auricle does not contain any Aschoff bodies. There is a moderate amount of interstitial fibrosis present. Small branches of the coronary arteries show moderate intimal thickening. The pericardial fat tissue is normal in amount. It does not show any evidences of inflammation. Some hypertrophy of the muscle fibers is present in the auricular and ventricular myocardium. There are no vascular occlusions. However, several sections reveal recent degenerative changes in the myocardium, in which the muscle fibers are almost completely absorbed and a loose young vascular connective tissue is taking their place. The appearance is similar to that occasionally found in recent myomalacia. This would indicate that small vascular occlusions are present, even though not in the sections examined. In some sections, the thickening of the blood vessel walls in the small coronary branches is rather marked. One section reveals a very pronounced thickening of the intima of one of the larger coronary branches, with almost complete occlusion of this vessel. In still another section in which more advanced diffuse myocardial scarring is present, this appears to be of somewhat longer duration, since the replacing connective tissue is more mature. Local myocardial fibers in these areas are markedly hypertrophied. Some sections show collections of plasma cells and occasional round cells in the pericardium. A phosphotungstic acid-hematoxylin stain on the thrombotic lesion on the mitral valve indicates it to be composed of fibrin and platelets with some hyalinization.

Lung. Sections of lung reveal a very markedly widened pleura, in which an advanced granulation tissue reaction with numerous new blood vessels, fibrosis, edema and round cell infiltration with macrophages is present. The pulmonary parenchyma is the seat of a confluent bronchopneumonia which involves most of the parenchyma, but the degree of the development of the pneumonia differs in different portions of the lung. There are several postinortal colonies of bacteria present. There are areas which show edema, others cellular exudation, and still others, fibrin. No occluded blood vessels are observed. Some branches of the pulmonary arteries show a moderate degree of arteriosclerosis.

Liver. Sections of the liver reveal a moderate amount of fat. The lobulation of the liver is normal. The parenchyma shows some autolytic changes with fragmentation of the liver cell cords. The blood vessels and bile ducts do not show any significant changes. There is a moderate amount of centri-lobular congestion, and there

is also some separation of the sinus walls from the liver cords. In one section of the liver, there is a small focal area of necrosis, containing broken down cells and pyknotic nuclei and a few polynuclear cells, and resembling somewhat a so-called "typhoid" nodule. Two or three such areas are present in this section.

Spleen. The capsule is covered with a few small clumps of fibrin. The capsule itself is not thickened. The splenic pulp shows a moderate increase in cellularity. The lymphoid follicles are normal in size and rather sharply outlined from the pulp. The sinusoids are markedly congested. The cellular increase in the red pulp appears to be due to an increase of all the normal cellular constituents of the spleen. There is no predominance of polynuclear cells. The blood vessels do not show any unusual changes. There are no infarcts.

Kidney. A considerable percentage of the glomeruli, perhaps two or three out of 10, contain hyaline masses in the glomerular capillaries. The basement membranes of the glomerular loops are thickened, and there is a suggestion of the so-called wire-loop appearance. The parenchyma shows a few small areas of focal atrophy, corresponding to the infarct scars described macroscopically. In these areas, the tubules are atrophic, the fibrous stroma is increased, and there is an infiltration by round cells. Some of these atrophic areas extend to the surface, as described macroscopically. The interlobular arteries, efferent and afferent arterioles, and the larger arcuate arteries, show moderate sclerotic changes, but no occlusion. The tubules of the kidney are fairly well preserved and the convoluted systems show some granular degeneration of the epithelial cells. Elastic Van Giesen stain does not disclose any other arterial lesions.

Pancreas. The parenchyma is normal in appearance. The ducts do not show any abnormalities. There is no increase of interstitial fat. The islet tissue is well preserved. The blood vessels are engorged. Section of the splenic arteries reveals rather marked intimal sclerosis.

Uterus. The endometrium appears in a resting phase, with moderate congestion of the stroma. The myometrium appears normal. There is no evidence of endometritis.

Ovary. There are a few small follicular cysts and growing follicles present. The ovarian stroma is injected. There are no histological evidences of inflammation.

Thymus reveals a moderate degree of physiologic atrophy of thymal tissue.

Skin. Sections of skin do not reveal any occlusive vascular lesions.

Lymph Nodes. The lymph nodes show some depletion of the small lymphocytes and there appears to be some *granulopoiesis* and lymphopoiesis going on within these nodes.

Retina. Section of retina and eyeball: Those blood vessels present in the section appear normal.

ANATOMICAL DIAGNOSIS

1. *Cause of Death:* Bronchopneumonia, generalized vascular occlusions.
2. Atypical verrucous endocarditis (Libman-Sacks).
3. Old rheumatic endocarditis, mitral and aortic valves.
4. Thrombo-endocarditis, mitral and aortic valves.
5. Uremia clinically, renal failure.
6. Diffuse hyaline thrombi of glomerular capillaries.
7. Numerous myocardial infarctions with scarring.
8. Lupus erythematosus.
9. Bilateral confluent bronchopneumonia, with acute fibrinous pleuritis.
10. Old pericarditis with moderate effusion.
11. Perihepatitis and perisplenitis.
12. Chronic passive congestion of liver and spleen.
13. Fibromyomata uteri.

COMMENT

The acquaintance of one of us with the disease designated today as atypical verrucous endocarditis by Libman and Sacks started in 1911 at Mt. Sinai Hospital, New York City. At that time Dr. Libman pointed out that there was a type of endocarditis associated with a skin lesion that resembled lupus erythematosus. Yet during all the intervening years this is to our knowledge the first case observed at Lebanon Hospital. Indeed the condition acute lupus erythematosus itself with accompanying endocarditis must also be rare for in a recent article—March 1933—Roxburgh⁴ stated that he could find only five such cases since 1906 in the records of St. Bartholomew's Hospital. At Mt. Sinai Hospital with its very extensive and efficient medical service, aware of the condition for several years, only 11 clear cut cases were available from a possible 37 cases up to the report of Dr. Louis Gross⁵ in Libman's Anniversary Volume II in 1933. Thus it can be said that the condition is particularly rare.

There are other types of verrucous endocarditis aside from the rheumatic and subacute bacterial which are classed in a large group of indeterminate endocarditides which include the cachectic and terminal forms.⁶ These do not belong in this category because they have a definite causative factor such as carcinomatosis, long standing debilitating infections and nephritis. Besides they have a different pathology.

The association of the endocarditis with lupus erythematosus has rendered it more fascinating, for the subject of skin and mucous membrane lesions in general disease is a feature of great interest and one that is frequently diagnostic. Perhaps a better understanding of the participation of the skin and mucous membranes in general physical states may be a great help in clinical diagnosis.

Hebra (in Volume I of the *Ztschr. der K. K. Gesellschaft der Aertzte* in 1845) described lupus erythematosus for the first time under the name *seborrhea congestiva* and again the same year in *Constatt's Jahresh. ü. d. Leistungen der Dermatologie in Jahre 1845*. Six years later M. Cazanave (1851) gave the disease its present name. In his atlas he describes the condition including it under affections of the sebaceous secretions.

In 1864 the Sydenham Press published a translation of Hebra's book on *Dermatology* by C. Hilton. This book of Hebra's formed a part of Virchow's *Handbuch der Speciellen Path. u. Therap.* Volume IV of this was published after Hebra's death by Kaposi in 1875 and it is to the latter author that we owe a very thorough investigation and description of the types of lupus erythematosus and particularly to the pointing out of the acute form. In Hebra's *Atlas* of 1856 two forms of the disease were pictured and described, the discoid and the aggregate. He considered it a local disease entirely. Since Kaposi's time, however, it is known to occur also as a general disease that may have grave consequences.⁷

We are not going further into Kaposi's description than to state that he

described the lesions of both chronic and acute lupus erythematosus and pointed out the possible transition from one to the other and the threatening nature of a wide dissemination of the lesions. He, in addition, gave a description of the pathology of the condition which closely resembles the descriptions of today, particularly that by Goeckerman⁸ of the Mayo Clinic. In 1872, in the *Arch. f. Dermat. u. Syph.*, Kaposi added to his description and included a new condition, *erysipelas perstans faciei*, which is an erysipelatous form of the disease arising usually on the basis of an old chronic lesion.

Among the 11 cases of acute lupus erythematosus described by Kaposi in his first article, he observed four deaths. In his conclusion he states that lupus erythematosus may be an acute or subacute condition with fever and widespread effect upon the general organism which may result in death. None of the cases, however, is described as having a cardiac lesion.

The modern discussion of the condition may well start with Osler's⁹ very extensive Goulstonian Lectures, published in the *Lancet* in 1885, on malignant endocarditis. Here are described all the forms and their pathology together with blood culture studies and the differentiation of the organisms recovered. This is the original description of both the acute and the subacute forms of malignant endocarditis and well deserves a perusal by anyone interested in a study of this disease. In the second of these lectures he mentions that this type of endocarditis occurs frequently in old and sclerosed valves and may run a more chronic course, thus mentioning for the first time the subacute form.

In 1895 in the *Am. Jr. Med. Sci.* Osler¹⁰ published the first of a series of articles on the visceral complications of erythema exudativa multiforme. There subsequently appeared articles in the *Brit. Jr. Derm.* (1900), *Am. Jr. Med. Sci.* (1904), and *Brit. Med. Jr.* (1914) where the final summary was given. He described in all a series of 29 cases. The skin lesions varied from urticaria to purpura, erythema exudativa multiforme, erythema nodosum and angio-neurotic edema. Some of the lesions may ulcerate. Patients may get well and have recurrences but the type of lesion may vary with each recurrence indicating the likelihood of the relationship of the lesions. Heart murmurs were often found and real rheumatic fever and chorea were frequent. Two of these 29 cases had skin lesions the description of which corresponds to acute lupus erythematosus—case 19 with lesions of lupus erythematosus and erysipelas-like eruption (Kaposi erysipelas perstans faciei), and case 26 with lupus erythematosus lesions. Both cases died with evidences of nephritis (case 26 succumbing in a second attack after recovery from the first). This case was seen by G. H. Fox and considered acute lupus erythematosus. This group of cases, is, no doubt, a polyglot one. Nowhere in the article does Osler mention verrucous heart lesions. He was not aware of them. One point which he does make, which rather points towards endocarditis, is that if albuminuria occurs, and particularly if nephritis is present, the cases are much more grave and the prognosis distinctly bad.

This seems to indicate the possible occurrence of the characteristic lesions later to be described.

In this connection it is interesting to note that many workers starting with Brocq. and extending down to the present time have considered the lesions of acute lupus erythematosus to be very similar to those of erythema multiforme (MacKenzie,¹¹ 1898; Galloway,¹² 1903).

In 1899 Fordyce¹³ reported a case of acute lupus erythematosus in the *Journal of Cutaneous and Genito-Urinary Disease* in which he for the first time described the capillary thromboses which are such a distinct feature of the cases here presented. The following year Fordyce and Holder¹⁴ in the *Medical Record* gave a very accurate description of these capillary thromboses in cases of lupus erythematosus and considered them the essential lesion of the disease. In this article, too, Fordyce, speaks of the aggravating effect of frost-bite and sunburn on the lesion as due to local injury. He states that "the disseminate form of the disease not infrequently simulates polymorphous erythema in its evolution and distribution and is at times accompanied by vesicular and bullous eruptions, fever and severe constitutional disturbances which are followed by death."

Holder examined 1000 sections, all taken from the discrete form and from all parts of the lesion. The pathology consisted of: (a) Perivascular round cell infiltration with the capillaries open and surrounded by leukocytes. The capillaries are dilated and irregular in outline. With time the cells become more and more packed until they finally encroach upon the lumen of the vessel. The cells finally degenerate, atrophy occurs and they disappear; (b) connective tissue changes. The upper corium is surrounded by irregular capillaries with collagenous tissue within looking grayish and swollen and suggesting coagulation necrosis, not staining with the usual dyes but staining with acid orcein; (c) secondary atrophy.

The literature on vascular thromboses of this type is scarce according to these authors. Leloir described them as endoangiitis obliterans. Unna denied their occurrence.

At the meeting of the American Dermatological Society at Princeton University in June 1898 Robinson denied that there were any such thromboses. In 1898, before the meeting of the British Medical Association in Edinburgh, Boeck stated that he had seen them. The authors saw them but were unable to determine the presence of an endarteritis. The sections were shown to E. K. Dunham who stated that he had not seen such lesions except in certain cases of nephritis. Since there is no evidence of blood clotting, he stated that he could not consider the condition a thrombosis and besides Weigert's stain showed no fibrin. He concluded that lupus erythematosus is a disease in which the blood supply is interfered with.

In 1903 Galloway and Macleod¹⁵ reported a case observed at Westminster Hospital by Colcott Fox and later by the authors at the Charing Cross Hospital which had bullous lesions and those of lupus erythematosus on the skin and mucous membranes together with a nephritis. This patient

had convulsions and at postmortem examination lung consolidation and pleurisy but no heart lesion. This case may have been one of those without endocarditis.

In 1914 Willy Schmidt¹⁶ reported three cases of acute lupus erythematosus. In this article he gave a table of the reported cases with the cause of death and the postmortem findings if done. Among these 33 cases there are two with heart valve lesions. One of Pernet's cases had vegetations on the mitral valve, pneumonia and renal involvement. The other is one of Feuerstein's which at postmortem examination showed verrucous endocarditis of the mitral valve and embolic nephritis. Many of the other cases showed pneumonia, pericarditis, pleuritis, nephritis, etc., but these two are selected as cases which were most probably atypical verrucous endocarditis. None of Schmidt's three cases, however, had any cardiac involvement but they all had pneumonia and one was stated to have had definite nephritis.

We cannot leave this subject without mentioning the mucous membrane lesions which Culver¹⁷ reported so ably in 11 cases in 1915. They are of great importance and it is our opinion that in some cases they may be the only lesions present. Indeed unexplained mouth lesions—ulcerations—with severe constitutional reaction should suggest the possibility of the diagnosis of erythema multiforme usually called by the dermatologists bullous although the bullae are often not seen because they have either disappeared or have left only their remnants.

Cases of this type, although they have sometimes been grouped under the erythema group of skin lesions, have been reported by Christian,¹⁸ Trimble,¹⁹ and by Jarcho.²⁰

The first case is placed together with this one because the pathological lesions were identical although the clinical picture was entirely different. Here there was no endocarditis and the pathological picture limited itself to the presence of hyaline thromboses of the smaller arterioles and capillaries.

Indeed this is the lesion that apparently produced all the visceral manifestations in both the cases here presented. If this is so the disease might be placed among the infections or intoxications, for thrombosis by conglutination of the red blood cells has been demonstrated notably by Ricker²¹ and later by Midsuno²² to be of this nature. Ricker pointed out that a toxin may cause stimulation of a smaller vessel which, if the stimulus is weak, will result in constriction of that vessel; but if stronger and continued, fatigue will follow with dilatation. If this stimulus is sufficiently strong and continued there may result a stoppage of the circulation. This will result in crowding or packing of the red blood cells within the vessel lumen. If this is long continued changes will take place in these packed or conglutinated cells. Finally fibrin will form so that there will be a real platelet clot as pointed out by Gross, although former authors did not so state. However, this mass undergoes hyaline degeneration obliterating the forms of the red blood cells and the fibrin and finally because of chemical change the whole is

rendered indistinguishable as a blood clot because no blood elements can be detected. Certainly blood pigment is not found in such thrombi.

Such thrombi were reported by several authors. Mallory²³ described them in the region of typhoid ulcers; Flexner²⁴ produced them experimentally with abrin and ricin poisoning; Boxmeyer²⁵ experimentally with hog cholera inoculations. Scriver and Oertel²⁶ have used this conception to explain bilateral cortical necroses of the kidneys in pregnancy with eclampsia, as also does Neuburger.²⁷ Moschcowitz described such a lesion of the cardiac vessels in a case of his mentioned before, the first of the cases reported here being an example of this disease.

Quite recently and for a period of years Schwartzman²⁸ has been describing a phenomenon of local reactivity that pathologically corresponds to the condition here described. It has been named the Schwartzman phenomenon. He found that if an excitant is injected into the skin some change takes place at the site so that a subsequent intravenous injection within 24 to 36 hours will result in necrosis at the altered skin site. Pathologically there is a thrombosis of the vessels at the site and an increased permeability of the vessels to blood elements, notably the red blood cells. Later he and other workers have been able to sensitize an organ, notably the kidney, and thereby produced lesions there. The use of testicular extract before the sensitization has enhanced its hemorrhagic effects. This Schwartzman phenomenon certainly suggests an explanation of the possible *modus operandi* of the formation of the lesions both in the skin and in the organs and accords rather well with Ricker's hypothesis of toxic effects upon the blood vessels.

Gross and Friedberg²⁹ and other co-workers of Gross have attempted to divide the cases of atypical verrucous endocarditis into types that correspond quite well to Schwartzman's work but whether this will stand the test of time is not known. They have renamed the condition non-bacterial thrombotic endocarditis and have in the series of articles accurately described the clinical and the pathological features.

One cannot fail to note some similarity of these cases to periarteritis nodosa. This has been pointed out more recently in the aforementioned articles of Friedberg and Gross.³⁰ In their paper on periarteritis nodosa they stress the possible relationship of rheumatic fever to periarteritis nodosa and the frequent occurrence of recent scarlet fever in these cases. Baehr³¹ spoke of the possible relationship of atypical verrucous endocarditis to periarteritis nodosa some time ago. Rose Spiegel³² did similarly lately. While periarteritis nodosa has a very much more distinct inflammatory reaction of the blood vessel wall and the periarterial tissues and while the cases here described showed little if any such reaction yet it may be that being thrombotic in the end in both cases they may be different stages of the same disease—periarteritis nodosa. Perhaps these cases are the most acute types of periarteritis nodosa, with lesions developing and death resulting before any of the real pathology of periarteritis nodosa develops. In Case 1 this could be

very satisfactorily adduced but in the case of the atypical verrucous endocarditis not so readily. In this latter case the course was very rapid but there are cases of a similar type in the literature that have lasted much longer,^{33, 44} and Libman and Sacks¹ have even suggested a possible cure from the observation of one case. Thus the acuteness of the condition could not here be stressed as the reason for the non-development of the lesions of periarteritis nodosa.

The polyglot lesions, the widespread organ involvement, the skin manifestations, the frequency of joint involvement, the febrile septic course, the frequent renal and cardiac involvement all speak for the possible association of the type of cases here described with periarteritis nodosa.

Lupus erythematosus may be acute or chronic. The chronic variety is also known as the discoid type and involves mainly the face in butterfly fashion over the nose and possibly also the hands. The moment there is a tendency to spread, the disease becomes menacing and is called acute and because it spreads to other parts of the body is called disseminate. The latter type may be present from the onset, or it may develop from the discoid type, or the acute type may become chronic, or the discoid may be acute in exacerbations. The lesions are polymorphic. They vary in the same individual in different attacks, being papular and erythematous in one attack and vesicular or bullous in another, or they may be of the erysipelas perstans faciei type during still another phase. The same holds true for the skin lesions of atypical verrucous endocarditis which may consist of urticaria, purpura, erythema multiforme, lupus or dermatomyositis at different times in the course of the disease. Two or three types of lesions may coexist.

Concerning the etiology of lupus erythematosus and therefore of atypical verrucous endocarditis little can be said of a conclusive nature. Tuberculosis has long been considered a cause, the name lupus being applied for that reason. Indeed tuberculosis is often found at autopsy—particularly glandular. Lymphadenopathy is a feature of the acute cases in particular. Keefer and Felty³⁴ took out one of these glands, macerated it, inoculated it into guinea pigs and recovered the tubercle bacillus. There are many authors, however, who do not consider tuberculosis the cause. Goeckerman³⁵ of the Mayo Clinic who has studied these cases exhaustively considers tuberculosis a predisposing cause.

Gennerich³⁶ believes that a sensitizing agent is produced in the glands by an unknown disease and that this agent has an especial affinity for the vascular system. This fits in with the idea of several authors that the cause may be any toxic agent.

Stokes³⁷ suggests that if a septic infection produces hypersensitiveness, a hematogenous tuberculous invasion results in a tuberculid and if tuberculosis produces the hypersensitiveness a septic blood invasion produces lupus erythematosus.

Recently Keil³⁸ made an analysis of all the cases in the literature and found the evidence rather against the tuberculous etiology. Most of the

cases reported either showed no tuberculosis or inactive tuberculosis at autopsy. He argues that inactive tuberculosis could not possibly be a cause.

In general it may be said that the European continental school favors the tuberculous etiology, the English school favors sepsis, especially streptococcal, and we in the United States favor a polyglot etiology including toxins and infections.³⁹

Acute extension of the disease may be produced by any surgical interference, by removal of teeth for foci of infection, by the injection of even very minute doses of tuberculin or vaccine, by the exhibition of gold compound (recently extensively used in the treatment of lupus erythematosus and tuberculosis), and by exposure to sunburn or windburn. All these exciting causes are important for they may be the stimulus for an extension of the disease which carries a very grave prognosis. The second case here described was exposed to sunburn which may have been the exciting cause of an extension of the disease which terminated in death.

The best description of the heart and vascular lesions is given by Gross in his article in Libman's Anniversary Volume II. The renal lesions were described by Baehr²⁸ and by Baehr and Sacks⁴⁰ and more recently again by Baehr³¹ in an article on the renal complications of endocarditis in the *Trans. of the Assoc. of American Phys. for 1931*. Both Libman and Baehr stress the possibility that this is a disease entity and Baehr mentions the possibility of its relationship to periarteritis nodosa although Manges and he⁴¹ have pointed out in the report of a case of periarteritis nodosa that the latter is definitely an inflammatory disease whereas these cases cannot definitely be stated to be inflammatory in nature. There is, however, one case in the literature of the association of lupus erythematosus with periarteritis nodosa.⁴²

The cases here described and the similar ones in the literature may not even be truly thrombotic—in the nature of a true platelet clot—despite the fact that Gross states them to be definite platelet thrombi and believes that the essential lesion is a swelling of the endothelial lining of the arterioles and capillaries. This in itself encroaches on the lumen of the vessel and leaves an eccentric slit. A hyaline thrombus often plugs the vessel, which Gross states to be definitely a platelet thrombus although a great many workers such as Flexner, Boxmeyer, Mallory and others did not consider it so. Efforts to demonstrate the nature of these hyaline thrombi as true thrombi were futile and no blood elements such as cells or blood pigment or fibrin could be demonstrated within them either chemically or histologically. The vessel may finally be channelled into one or two lumens, the latter by a fibrous bar across the vessel.

The heart lesion is a flat lesion made up mainly of a coalescence of the rather fine verrucous lesions that are found mainly on the ventricular aspect of the mitral valve and on the adjacent ventricular mitral endocardium. Gross has called this the "pocket lesion." The verrucae on the valve may vary in size and are found mainly along the closure line. The lesions are

definitely thrombotic and some have called the condition a thromboendocarditis. The valve is not vascularized if there has been no previous rheumatic fever. In our Case 2 there was a definitely active rheumatic fever coincident with the disease. This lack of vascularization of the valves, besides the absence of Aschoff bodies, has been one of the pathological differential points from rheumatic fever.

Further to differentiate this disease from rheumatic fever is the valve involvement which is mainly mitral in both but is almost as frequently pulmonary and tricuspid in atypical verrucous endocarditis, whereas in rheumatic fever the other valve usually involved is the aortic with the pulmonary valve very rarely involved.

To differentiate the disease from subacute bacterial endocarditis there is the type of valve involvement, the pericarditis, the frequency of bronchopneumonia, the negative blood culture and the azotemic glomerulonephritis without the Baehr-Lohlein glomerular lesions—the so-called crescents, etc.

This disease may heal with sclerosis of the valves and these may be the seat of future subacute bacterial endocarditis as pointed out by Libman.

A recent report by Belote and Ratner⁴³ with a review of the literature points out that the disease may occur without endocarditis. Indeed if the disease is considered to be a general one then any organ in the body may or may not be involved and the occurrence of atypical verrucous endocarditis places it in a subgroup of the general disease now called Libman-Sacks disease. Indeed this fact of no cardiac involvement was pointed out by the Mt. Sinai workers before. If this is so then the whole group of cases of acute lupus erythematosus disseminatus with visceral manifestations may form a unit and represent one disease. Belote and Ratner did not find the vascular lesions in their case and it is, therefore, difficult to place it exactly.

The first case is of interest because up to the time of the report of this case (1932) only one case was reported in the literature, that of Moschowitz, although since there have been more^{28, 33, 44} and because as previously stated the vascular lesions are similar in the two. This case had no endocardial lesion. In this case there was very extensive involvement of the smaller coronary vessels, yet the clinical picture of the disease was that of acquired hemolytic jaundice and thrombocytopenic purpura. In a very recent article Keil³⁸ discusses the relationship of lupus erythematosus and thrombocytopenic purpura. The case here reported had no lupus erythematosus but did have the "hyaline thrombi" that Keil speaks of in his case report and in the discussion. As a possible cause of the thrombopenia Keil mentions the removal of the platelets by participation in the formation of the thrombi. Against this, of course, is the fact that such removal in the body would stimulate new formation of the platelets from the megakaryocytes of the bone marrow. This would necessitate the assumption of depression of this function at the same time, or splenic destruction to further the theory. However, aside from this the hyaline thrombi have not definitely been proved to be platelet thrombi despite statement to the contrary.

Is it possible that there exists a toxemia or an infection that has an especial affinity for the endothelium of the arterioles and capillaries and thereby causes a bizarre clinical picture depending on the particular location of the lesions? Or are we to agree with Ricker that such affinity in itself is not necessary and that the stimulus of such toxemia or infection is sufficient to paralyze the vessels—as it were—and to result in conglomerative thrombi which are really not thrombi at all but only packed cells?

Did either of these causes in the first case attack the vessels of the bone marrow and result in the peculiar thrombocytopenia, hemorrhagic diathesis, reticulocytosis, jaundice, and anemia, and did it in addition attack the nutrient vasa vasorum of the various vessels resulting in their peculiar permeability to the blood elements, or were these hemorrhages the results of the thrombosis with rupture of the vessels as is so well seen in periarteritis nodosa? These questions cannot now be answered.

As pointed out, Schwartzman has attempted an explanation by his phenomenon of tissue reactivity of both the thrombocytopenia and the permeability of the blood vessels.

REFERENCES

1. LIBMAN, EMANUEL: Some general considerations concerning affections of the valves of the heart, *Med. Clin. North Am.*, 1917, i, 573-590.
- LIBMAN, EMANUEL, and SACKS, BENJAMIN: A hitherto undescribed form of valvular and mural endocarditis, *Trans. Assoc. Am. Phys.*, 1923, xxxviii, 46-61. Abstract—*Jr. Am. Med. Assoc.*, 1923, lxxx, 1724.
- LIBMAN, EMANUEL, and SACKS, BENJAMIN: Atypical verrucous endocarditis, *Proc. New York Path. Soc.*, 1923, xxiii, 69-74.
- LIBMAN, EMANUEL, and SACKS, BENJAMIN: A hitherto undescribed form of valvular and mural endocarditis, *Arch. Int. Med.*, 1924, xxxiii, 701-737.
2. MOSCHCOWITZ, ELI: Hyaline thrombosis of the terminal arterioles and capillaries: a hitherto undescribed disease, *Proc. New York Path. Soc.*, 1924, xxiv, 21-24.
- MOSCHCOWITZ, ELI: An acute pleiochromic anemia with hyaline thrombosis of the terminal arterioles and capillaries, *Arch. Int. Med.*, 1925, xxxvi, 89-93.
3. DAVIS, DAVID, and AYONEN, DAVID: Subacute bacterial endocarditis with unusual vesiculobullous skin lesions: necropsy reports of 2 cases, *Am. Heart Jr.*, 1927, ii, 671-681.
4. ROXBURGH, A. C.: Acute disseminated lupus erythematosus: 5 fatal cases, *Brit. Jr. Dermat. and Syph.*, 1933, xlv, 95-109.
5. GROSS, LOUIS: The heart in atypical verrucous endocarditis (Libman-Sacks), *Libman's Anniversary Volume*, 1932, ii, 527-550.
6. LIBMAN, EMANUEL: Characterization of the various forms of endocarditis, *Jr. Am. Med. Assoc.*, 1923, lxxx, 813-818.
7. KAPOSI (MORITZ KOHN): Neue Beiträge zur Kenntnis der Lupus Erythematosus, *Arch. f. Dermat. u. Syph.*, 1872, iv, 36-78.
8. GOECKERMAN, WM. H., and MONTGOMERY, HAMILTON: Lupus Erythematosus. An evaluation of histopathological examinations, *Arch. Dermat. and Syph.*, 1932, xxv, 304-316.
9. OSLER, SIR WILLIAM: Malignant endocarditis (Goulstonian Lectures), *Lancet*, 1885, i, 415-418; 459-466; 505-508.
10. OSLER, SIR WILLIAM: On the visceral manifestations of erythema exudativum multiforme, *Am. Jr. Med. Sci.*, 1895, cx, 629-646.

- OSLER, SIR WILLIAM: The visceral lesions of the erythema group (2nd series of cases), *Brit. Jr. Dermat.*, 1900, xii, 227-245.
- OSLER, SIR WILLIAM: On the visceral manifestations of the erythema group of skin diseases, *Am. Jr. Med. Sci.*, 1904, cxxvii, 1-23.
- OSLER, SIR WILLIAM: The visceral lesions of purpura and allied conditions, *Brit. Med. Jr.*, 1914, i, 517-525.
11. MACKENZIE, STEPHEN: Case of local asphyxia, acne neurotica and lupus erythematosus, *Brit. Jr. Dermat.*, 1898, x, 10-11.
 12. GALLOWAY, JAMES: In report of meeting of Dermatological Soc. of London Med., Jan. 12, 1898. *Brit. Jr. Dermat.*, 1898, x, 49-50.
CAVAFY, JOHN: In report of meeting of same society March 9, 1898, p. 139-140.
 13. FORDYCE, J. A.: Lupus erythematosus in a tuberculous subject, *Jr. Cutan. and G. A. Dis.*, 1899, xvii, 113-116.
 14. FORDYCE, J. A., and HOLDER, O. H.: Some clinical observations on lupus erythematosus; the pathology of lupus erythematosus, *Med. Rec.*, 1900, lviii, 41-48.
 15. GALLOWAY, JAMES, and MACLEOD, J. M. H.: Erythema multiforme and lupus erythematosus; their relationship to general toxemia, *Brit. Jr. Dermat.*, 1903, xv, 81-94.
 16. SCHMIDT, WILLY: Ueber drei Faelle von Lupus Erythematosus Acutus nebst statistischen Beiträgen zur Lehre dieser Krankheit und Besprechung der Aetiologie derselben, *Dermat. Ztschr.*, 1914, xxi, 28-65.
 17. CULVER, GEORGE D.: Lupus erythematosus of the mucous membranes, *Jr. Am. Med. Assoc.*, 1915, lxv, 773-778.
 18. CHRISTIAN, HENRY A.: Long continued fever with inflammatory changes in serous and synovial membranes and eventual glomerulonephritis. A clinical syndrome of unknown etiology, *Med. Clin. North Am.*, 1935, xix, 1023-1026.
 19. TRIMBLE, I. RIDGEWAY: Erythematous group of skin diseases with especial reference to abdominal pain, *Jr. Am. Med. Assoc.*, 1931, xcvi, 2010-2014.
 20. JARCHO, SAUL: Lupus erythematosus associated with visceral vascular lesions, *Bull. Johns Hopkins Hosp.*, 1936, lix, 262-274.
 21. RICKER, GUSTAV: Pathologie als Naturwissenschaft-Relations-pathologie, 1924, 42-52; 98; 188; 193.
RICKER, GUSTAV: Die Methode der direkter Beobachtung der lokalen Kreislaufs Störungen und die Verwertung pathologisch-anatomische Befunden Kreislaufs Organen für die Pathologie derselben, *Handb. d. biologischen Arbeitsmethoden*, 1924, viii, Teil 1, Hefte 1.
 22. MIDSUNO, REHSI: Beiträge zur Morphologie und Physiologie der terminalen Blutbahn, *Beitr. z. Path. Anat.*, 1930, lxxxiv, 183-230.
 23. MALLORY: Cited by Flexner.²⁴
 24. FLEXNER, SIMON: On thrombi composed of agglutinated red blood cells, *Jr. Med. Res. (n.s.)*, 1902, iii, 316-321.
 25. BOXMEYER, CHARLES H.: A study of the necroses occurring in the liver of experimental animals after inoculation with hog cholera bacilli, *Jr. Med. Res. (n.s.)*, 1903, iv, 146-163.
 26. SCRIVER, WALTER DE M., and OERTEL, HORST: Necrotic sequestration of the kidneys in pregnancy (symmetrical cortical necrosis), *Jr. Path. and Bact.*, 1930, xxxiii, 1071-1094.
 27. NEUBURGER, KARL: Ueber angiospastische nichtembolische Entstehung von Niereninfarkten und von Extremitätengangrän, *Virchow's Arch. f. path. Anat. u. Physiol.*, 1927, cclxv, 789-804.
 28. SCHWARTZMAN, GREGORY, KLEMPERER, PAUL, and GERBER, ISIDORE E.: The phenomenon of local tissue reactivity to bacterial filtrates (the rôle of arteriolar vascular responses in certain human diseases), *Jr. Am. Med. Assoc.*, 1936, cvii, 1946-1951.
SCHWARTZMAN, GREGORY: Libman's Anniversary Volume, 1932.
 29. GROSS, LOUIS, and FRIEDBERG, CHARLES K.: Non-bacterial thrombotic endocarditis. Classification and general description, *Arch. Int. Med.*, 1936, lviii, 620-640.

- FRIEDBERG, CHARLES K., and GROSS, LOUIS: Non-bacterial thrombotic endocarditis associated with acute thrombocytopenic purpura, *Arch. Int. Med.*, 1936, lviii, 641-661.
- FRIEDBERG, CHARLES K., GROSS, LOUIS, and WALLECH, KAUFMAN: Non-bacterial thrombotic endocarditis associated with prolonged fever, inflammation of serous membranes, and widespread vascular lesions, *Arch. Int. Med.*, 1936, lviii, 662-684.
30. FRIEDBERG, CHARLES K., and GROSS, LOUIS: Periarthritis nodosa (necrotizing arteritis) associated with rheumatic heart disease (with a note on abdominal rheumatism), *Arch. Int. Med.*, 1934, liv, 170-198.
31. BAEHR, GEORGE: The renal complications of endocarditis, *Trans. Assoc. Am. Phys.*, 1931, xlv, 87-95.
- BAEHR, GEORGE, KLEMPERER, PAUL, and SCHIFRIN, ARTHUR: A diffuse disease of the peripheral circulation (usually associated with lupus erythematosus and endocarditis), *Trans. Assoc. Am. Phys.*, 1935, 1, 139-155.
32. SPIEGEL, ROSE: Clinical aspects of periarthritis nodosa, *Arch. Int. Med.*, 1936, lviii, 993-1040.
33. WISE, FRED: The relation of lupus erythematosus and tuberculosis, *New York Med. Jr.*, 1918, cvii, 1164-1167.
- ZUMBUSCH, L. V.: Zur Ätiologie des Lupus Erythematodes, *Arch. f. Dermat. u. Syph.*, 1925, cxlix, 136-141.
34. KEEFER, CHESTER S., and FELTY, AUGUSTUS R.: Acute disseminate lupus erythematosus. Report of 3 fatal cases, *Bull. Johns Hopkins Hosp.*, 1924, xxxv, 294-304.
35. GOECKERMAN, WM. H.: Lupus erythematosus as a systemic disease, *Jr. Am. Med. Assoc.*, 1923, lxxx, 542-547.
36. GENNERICH, WILHELM: Ueber die Ätiologie des Lupus Erythematodes, *Arch. f. Dermat. u. Syph.*, 1921, cxxxv, 184-207.
37. STOKES, JOHN N.: The diagnosis of disseminate erythematous lupus, *Med. Clin. North Am.*, 1926, x, 290-294.
38. KEIL, HARRY: Relationship between lupus erythematosus and tuberculosis, *Arch. Dermat. and Syph.*, 1933, xxviii, 765-779.
39. WISE, FRED: The relation of lupus erythematosus and tuberculosis, *New York Med. Jr.*, 1918, cvii, 1164-1167.
- ZUMBUSCH, L. V.: Zur Ätiologie des Lupus Erythematodes, *Arch. f. Dermat. u. Syph.*, 1925, cxlix, 136-141.
40. BAEHR, GEORGE, and SACKS, BENJAMIN: The occurrence of glomerulonephritis in association with verrucous endocarditis, *Proc. New York Path. Soc.*, 1923, xxiii, 64-69.
41. MANGES, MORRIS, and BAEHR, GEORGE: Periarthritis nodosa, *Am. Jr. Med. Sci.*, 1921, clxii, 162-182.
42. VOLK, R.: Periarthritis nodosa bei einem Lupus Erythematodes Chronica cum Exacerbatione, *Dermat. Ztschr.*, 1928, liii, 682-691.
43. BELOTE, GEORGE H., and RATNER, H. S. V.: The so-called Libman-Sacks syndrome. Its relation to dermatology, *Arch. Dermat. and Syph.*, 1936, xxxiii, 642-664.
44. HOLLANDER, LESTER, KASTLIN, GEORGE J., FISHER, A., and SCHLESINGER, CLARA R.: Lupus erythematosus subacutus with an unusual blood picture. (A clinical study), *Arch. Dermat. and Syph.*, 1932, xxv, 353-364.

CASE REPORTS

SCHÜLLER-CHRISTIAN'S DISEASE; REPORT OF A CASE IN ONE OF IDENTICAL TWINS *

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SCHÜLLER-CHRISTIAN'S disease is a constitutional metabolic disorder. It does not appear to be familial nor hereditary. Identical twins have identical heredity and, barring intrauterine and birth accidents, are born with identical constitutions. Theoretically, they should be equally susceptible to disease and under the same environmental conditions should have the same illnesses with equal severity at the same time. Judging from the reports appearing in the literature this seems to be the case. With rare exceptions in all the cases reported in which a disease has occurred in one identical twin, the same disease has occurred approximately simultaneously in the other.

CASE REPORT

Betty M. and a twin sister were born at full term on March 3, 1934. The ancestry was Scotch-Irish, Scandinavian and Spanish. Labor was uneventful and not difficult. There were two older brothers, aged 6 and 4 years. Her birth weight was $5\frac{15}{16}$ pounds. Growth and development had been normal and, except for a moderately severe attack of measles at $1\frac{1}{2}$ years and an occasional "cold," she had been well until the onset of the present illness.

In November 1936, a soft area was discovered in that region of the skull formerly occupied by the anterior fontanelle. The parents are positive the fontanelle had closed several months previously. The area was slightly elevated and free from pain and tenderness. There had been no subjective symptoms until this time, but listlessness, slight irritability and somnolence were soon noted. The bone defect gradually increased in size and, in the latter part of December, pain and tenderness appeared in the upper left arm. There was no limitation of motion of the left shoulder joint. On January 12, 1937, she came under observation and was admitted to hospital on the same day. On physical examination she was a delicate appearing child, slightly small for her age and somewhat listless. Weight 30 pounds. There was a soft, irregularly shaped area with rough edges, approximately 4 cm. by 7 cm. in the vertex of the skull at the junction of the sagittal and coronal sutures. This area did not appear to be in the least tender, was slightly raised and on palpation gave the impression of a semisolid mass under moderate tension. The upper third of the left humerus was enlarged and slightly tender, the enlargement increasing from below upward. Blood counts were normal and urinalyses were negative. Blood cholesterol and calcium were 166.1 mg. and 11.6 mg. per 100 c.c. of whole blood, respectively. A roentgenogram of the skull confirmed the finding of an area of bone destruction and showed destruction of the periosteum as well as of the cortex. A roentgenogram of the

* Received for publication July 9, 1938.

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upper half of the left humerus showed extensive destruction of bone and of periosteum along the medial border, destruction of the shaft in the involved area and moderate thickening of the periosteum below the area where the periosteum was destroyed. Complete roentgen studies of the remainder of the skeleton were negative.

A large needle was inserted into the skull lesion in an attempt to obtain material for biopsy. A single minute piece of tissue was obtained in addition to bloody fluid. Smears made from the fluid showed nothing more than would be found in fluid

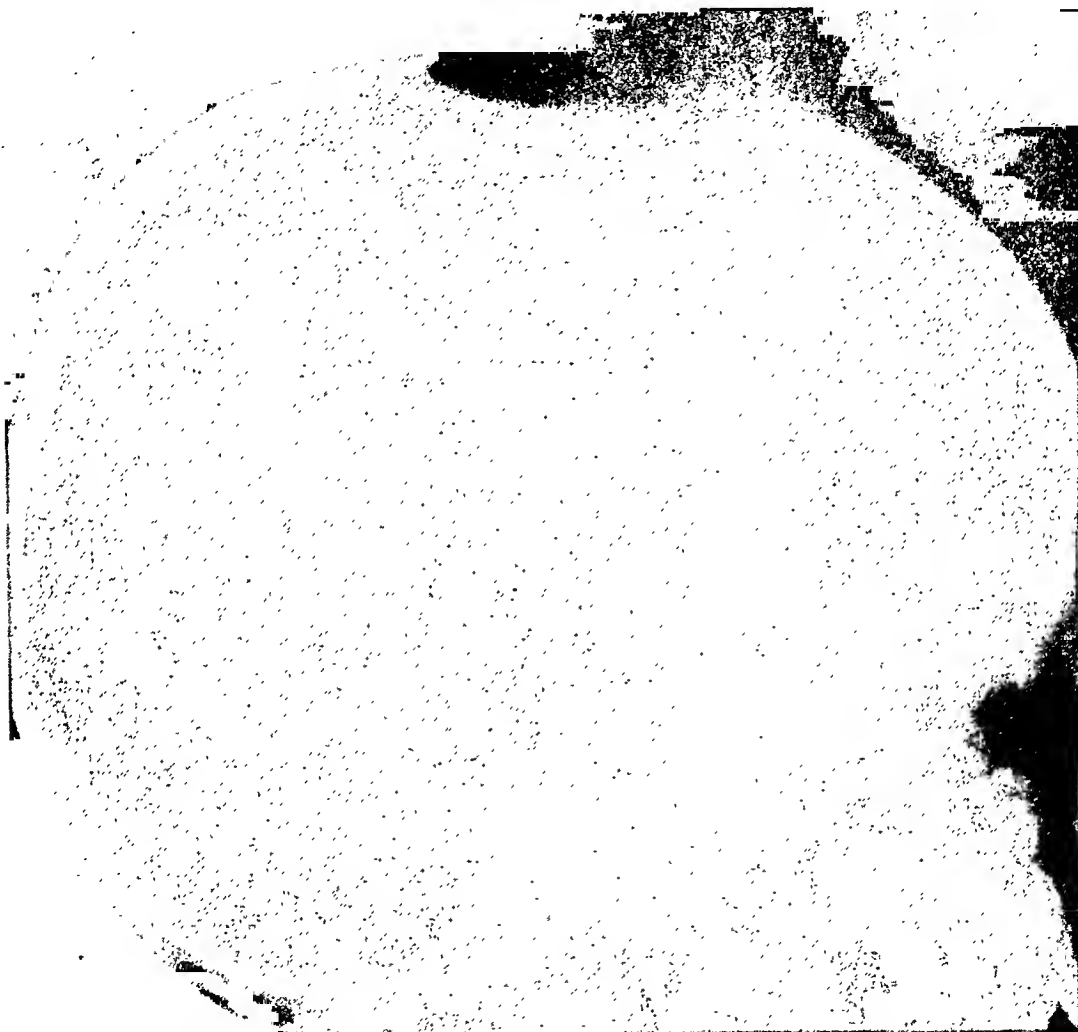


FIG. 1. Roentgenogram made March 25, 1937, showing osteolytic area in the vertex of the skull.

aspirated from any bone marrow. Histologically the small piece of tissue was very vascular and resembled periosteum. The endothelium lining the vessels was markedly thickened, clear and glassy in appearance. In the surrounding exudate were numerous granulocytic cells, the majority of which were eosinophilic. Large histiocytes, some of them actively phagocytic for leukocytes and debris, were present. Other large foamy cells, containing a small amount of pigment, which gave a positive reaction for iron, were present. Multinucleated giant cells of the foreign body type were also found in small numbers in the exudate.

Three days after admission she became acutely ill with fever, vomiting and

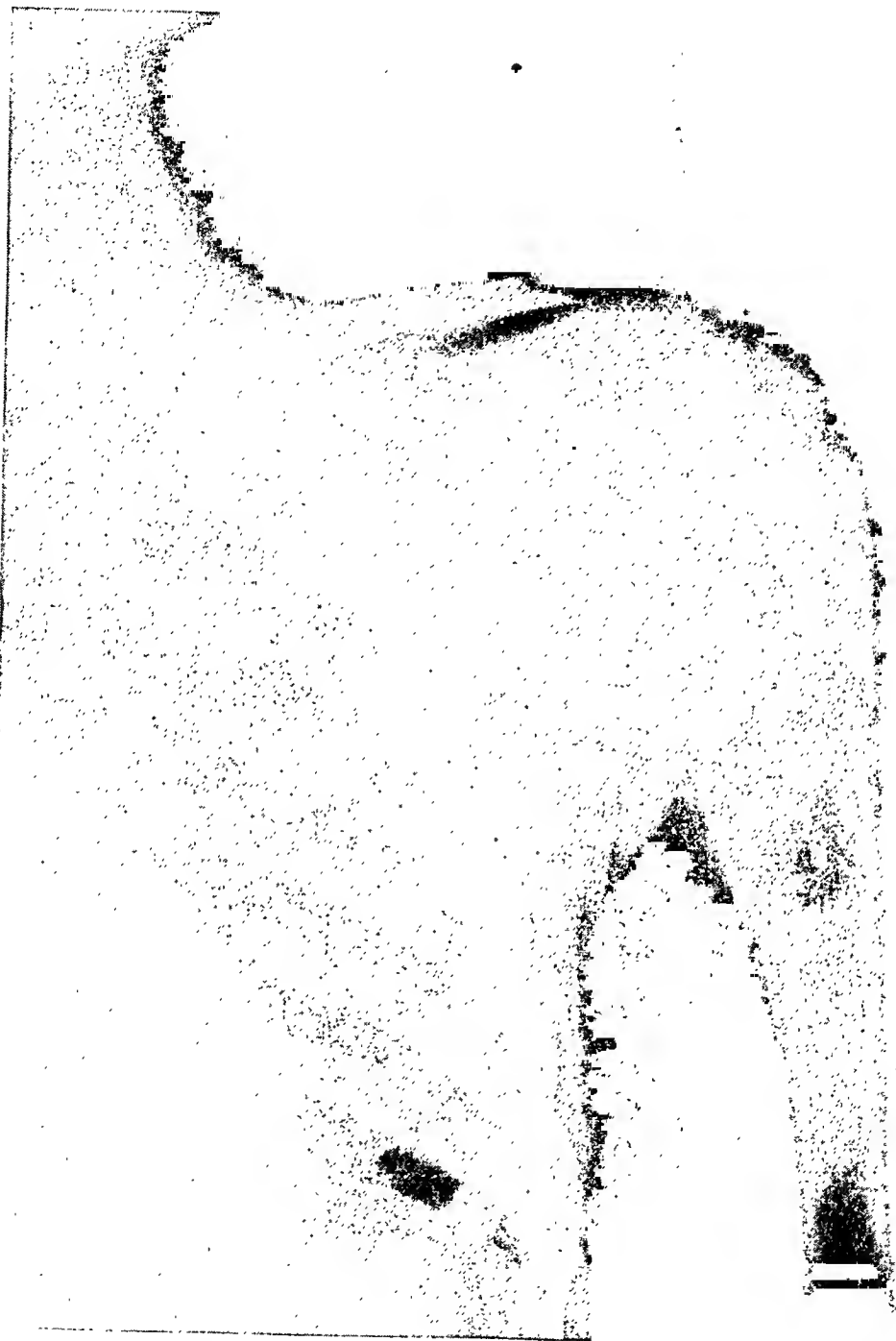


FIG. 2. Roentgenogram made January 14, 1937, showing osteolytic area in the upper half of the humerus.

leukocytosis. Diagnosis of bilateral, acute, purulent otitis media was made. Following bilateral myringotomy the acute symptoms promptly disappeared.

Treatment and Progress: Treatment has consisted of roentgen-ray therapy and general hygienic measures. A course of six daily roentgen-ray applications to the bone lesions was given, beginning February 1, 1937. During the first month she was under observation, listlessness, peevishness, lack of appetite with occasional vomiting

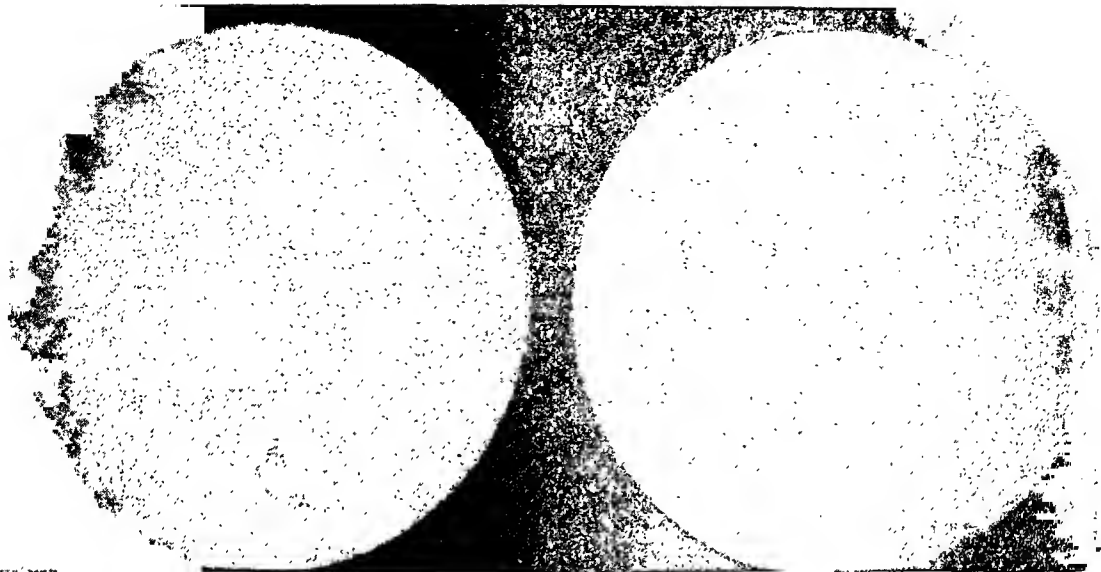


FIG. 3. Roentgenogram made May 14, 1937, showing osteolytic area involving posterior half of the right mastoid area.

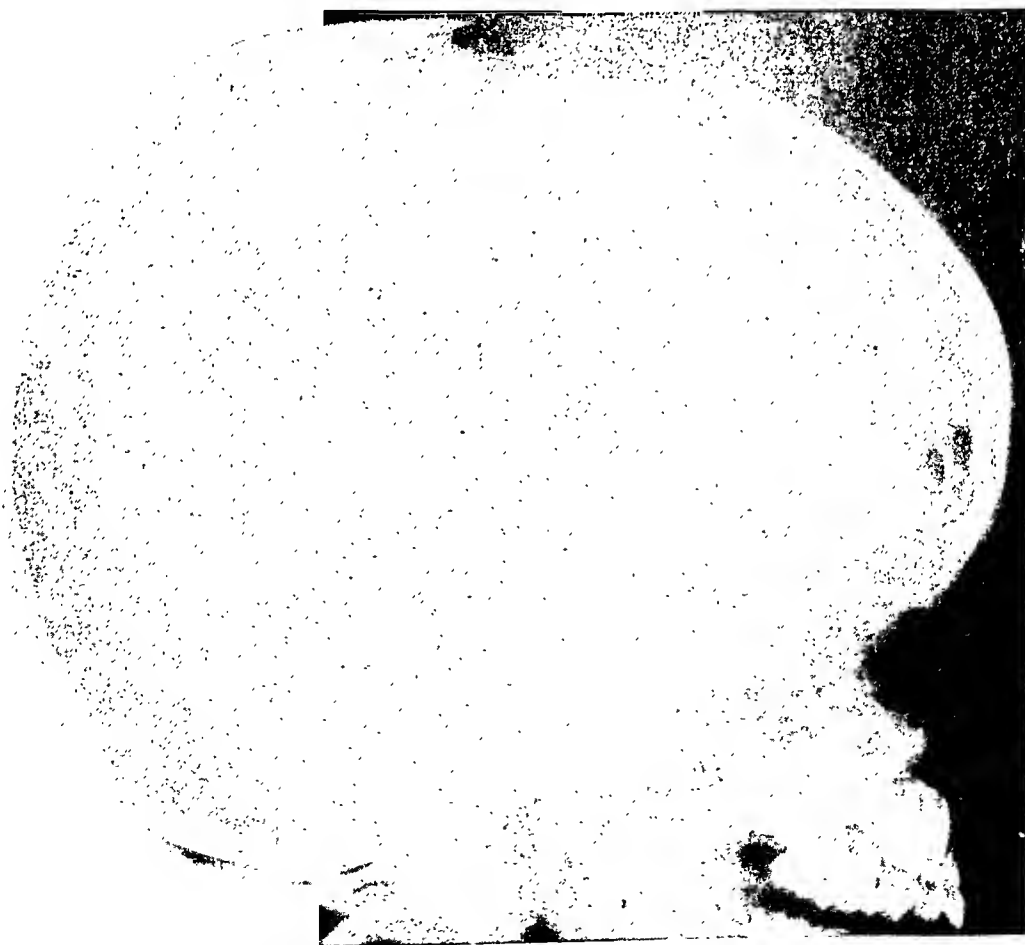


FIG. 4. Roentgenogram made June 14, 1937, showing new area of osteolysis in the parietal bones.

and loss of weight continued. The symptoms then subsided, she began to improve in general appearance and quickly regained the weight she had lost. Within a month after the beginning of treatment the skull defect was softer and slightly depressed, and a roentgenogram made March 22 showed definite reossification in the involved area of the left humerus and to a somewhat lesser degree in that of the skull. On March 23 a small cartilage-like tumor was discovered in the right external ear canal. This was removed and subjected to histological study. Microscopically this tumor was very similar to the piece of tissue removed earlier from the bone lesion in the skull. In April she complained of severe vertigo and was unable to stand because

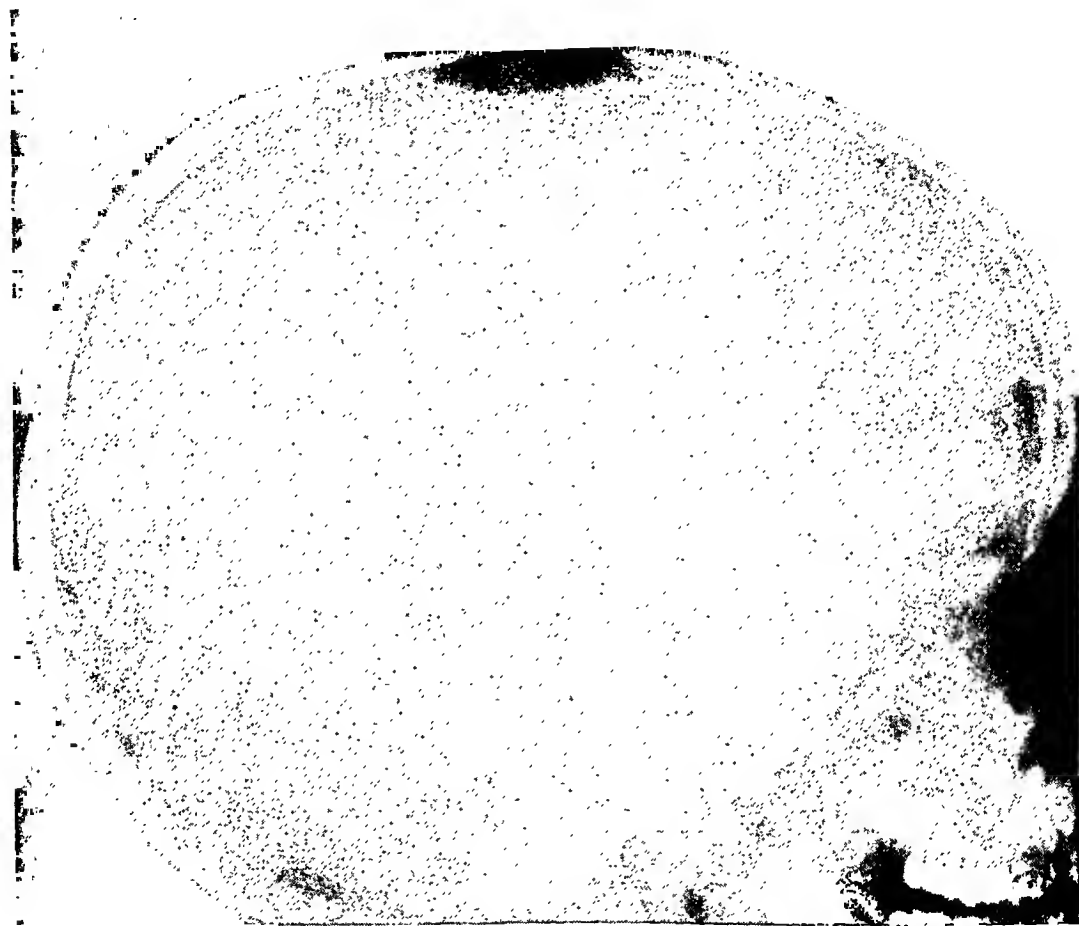


FIG. 5. Roentgenogram made January 3, 1938, showing considerable regeneration of bone in the original defect and complete disappearance of small parietal bone defects.

of this symptom. Roentgenogram showed an area of bone destruction involving the posterior half of the right mastoid area with extension medially into the petrous ridge. Roentgen therapy was given immediately. Within 10 days the vertigo had completely disappeared and five weeks later reossification of the temporal bone lesion was noted. In June she became listless and somnolent. On roentgen-ray examination two small bone defects were found in the parietal bones, one on each side just lateral to the original skull defect. These were subjected to roentgen-ray applications immediately. Within a week the subjective symptoms had disappeared and films made four months later showed no evidence of these defects. Since June 1937, there has been no further specific treatment and no evidence of new lesions. There has been steady growth and gain in weight. When compared with her healthy twin she ap-

pears normal and there has been no retardation in mental and physical development. Roentgenograms made December 31, 1937 show complete disappearance of the smaller defects in the parietal bone, marked reossification in the lesion in the left humerus



FIG. 6. Roentgenogram made December 30, 1937, showing marked regeneration of bone in the left humerus.

and somewhat less marked reossification in the original skull defect. Roentgenograms made May 3, 1938 show still further improvement.

Proof of Identity. Betty, the patient, was born first. Judy, born six minutes later, weighed 5½ pounds. The placenta and its membranes were examined carefully and consisted of one placenta, one chorion and two amnions. Before the onset

of Betty's present illness the children were strikingly similar in physical appearances, tastes, likes, dislikes, dispositions and mental development. This was so marked the mother had great difficulty in distinguishing one from the other during the first year. The only way she could be certain was by examination of the growth of the hair on the occiput. Betty had two whorls, Judy one. The father was obliged to resort to this procedure until they were more than two years of age. The color and texture of the skin and hair and the pigmentation of the iris were identical. The form of the face, ears, hands, nails and body build showed strong resemblances. From birth, except during the illness in January and February 1937, referred to above, Betty had weighed from one-half to one pound more than Judy. Judy on the other hand had always been slightly taller. This had never exceeded one inch. They had had the same illnesses (measles and acute respiratory infections) at the same time and with the same severity. The finger prints were not identical but showed greater similarity than is ordinarily seen even in members of the same family. They were reported as being of the "same type print on the corresponding finger, the inner and outer termini on corresponding prints are in the same locality and the ridge counts on prints from corresponding fingers are approximately the same." The dental examination showed the greatest similarity. "The occlusion showed striking resemblance with a slightly more than normal overbite of the upper teeth, probably the result of thumb-sucking of which there was a history. There was a marked deviation from the normal in the shape of the lower first molars. This abnormality, which occurs in both, consists of a marked increase in the antero-posterior dimensions when compared with the linguo-labial width. Deviation of the usual cuspal forms was also noticeable and identical. The second lower molars more nearly resemble, in shape and size, permanent teeth than those usually found in the first dentition; these, too, are identical for the two girls." They belong to the same blood group. Blood chemistry studies gave the following figures (expressed in mg. per 100 c.c. of whole blood):

	<i>Betty</i>	<i>Judy</i>
Cholesterol	140.0	142.3
Calcium	10.9	10.7
Phosphorus	3.2	2.8
Head measurements in cm.:	<i>Betty</i>	<i>Judy</i>
Length (forehead to occiput)	16 $\frac{3}{4}$	17 $\frac{1}{2}$
Width	13 $\frac{3}{4}$	13 $\frac{1}{2}$
Circumference	48	48

DISCUSSION

The case is presented as one of xanthomatosis of the Schüller-Christian type. The age of the patient, the clinical picture and the course of the disease leave little doubt as to the correctness of the diagnosis. While two of the three symptoms characteristic of the disease—diabetes insipidus and exophthalmos—are not present, other undoubted cases have been reported in which bone defects were the only symptoms. These were thought to have been mild, and in some instances, early cases as this case appears to be. The microscopic findings of an abundance of large foamy cells characteristic of the active stage of the disease were not seen in the small piece of tissue removed but we are not certain that the section came from the actively growing granuloma-like tissue mass and the findings were consistent with those of the chronic form of the disease or tissue from the area immediately surrounding an active lesion. The blood cholesterol was not increased, at the time it was measured, but this is true of approximately 50 per cent of the reported cases in which this estimation was made.

Also there is little doubt as to monozygosity of the twins. They meet all the requirements for its establishment. After treatment Betty lost her hair completely and it came back much darker in color so that differentiation is easily made now.

This case is reported, primarily, for its interest to the geneticist. If Schüller-Christian's disease is a constitutional disorder and the accepted opinion as to the production of identical twins is correct then Judy should have developed the disease before this time. Their environmental conditions were as nearly the same as was possible from birth to the onset of the disease.

Of secondary interest is the improvement following, and apparently attributable to, roentgenotherapy. There appears to have been some relation between promptness of response of the bone lesions to treatment and length of time from onset to beginning of treatment. The longer the lesions had existed before treatment was instituted the slower the reossification.

The possibility that the disease may appear in the healthy twin is recognized and she is being carefully studied at frequent intervals for its appearance. Examination made in May 1938, including roentgenograms of the skull, was entirely negative for any evidence of disease.

A CASE OF HEMOCHROMATOSIS WITH ALMOST COMPLETE ABSENCE OF SKIN PIGMENT, AND WITH FATAL RUPTURE OF AN ESOPHAGEAL VARIX*

By MAYNARD E. HOLMES, M.D., F.A.C.P., *Syracuse, New York*

HEMOCHROMATOSIS, also known as bronzed diabetes and pigment cirrhosis, is said to be a rare disease. Sheldon³ in his recent book on hemochromatosis has made a most thorough and extensive review of the literature. In his painstaking search he was able to collect 311 cases which could be accepted as genuine instances of the disease. He cites Stewart as having collected records of but 52 cases of hemochromatosis from 38,095 autopsies performed in several British hospitals. In Bellevue hospital in New York City only four cases of this disease were noted in 5000 autopsies.¹ Butt and Wilder² have recently reported 30 instances of hemochromatosis seen at the Mayo Clinic over a period of 15 years.

The classical triad of this disease often mentioned is pigmentation of the skin, diabetes, and cirrhosis or enlargement of the liver. There is deposition of the pigments hemosiderin and hemofuscin in various organs and tissues of the body, notably the liver, pancreas, spleen, abdominal lymph nodes, heart muscle and adrenals. This phenomenon is accompanied by extensive fibrosis and sclerosis of the tissues subjected to this abnormal deposition of pigment. These changes in the liver finally bring about hepatic cirrhosis with damage to the portal circulation, and in the pancreas the process is no doubt related to the development of diabetes. The melanosis often present is said to result from the fibrous replace-

* Received for publication June 29, 1938.

The author is indebted to Dr. Shields Warren of Boston for having reviewed the microscopic sections from this case and for his helpful comment. In making the photomicrographs the background cellular structures were sacrificed somewhat to bring out the pigment more clearly.

ment which occurs in the zona glomerulosa of the adrenal, and similar changes in the anterior pituitary may explain the gonad hypoplasia which has been frequently described.

Despite many attempted solutions the etiology of hemochromatosis must still be considered an enigma. The consensus at present seems to be that this disease, which takes many years to develop, is due to an inborn error in cellular metabolism.

CASE REPORT

A man, aged 55 years, was first seen on January 15, 1937, with a history of loss of weight and a tendency to drowsiness of four months' duration. He had felt well

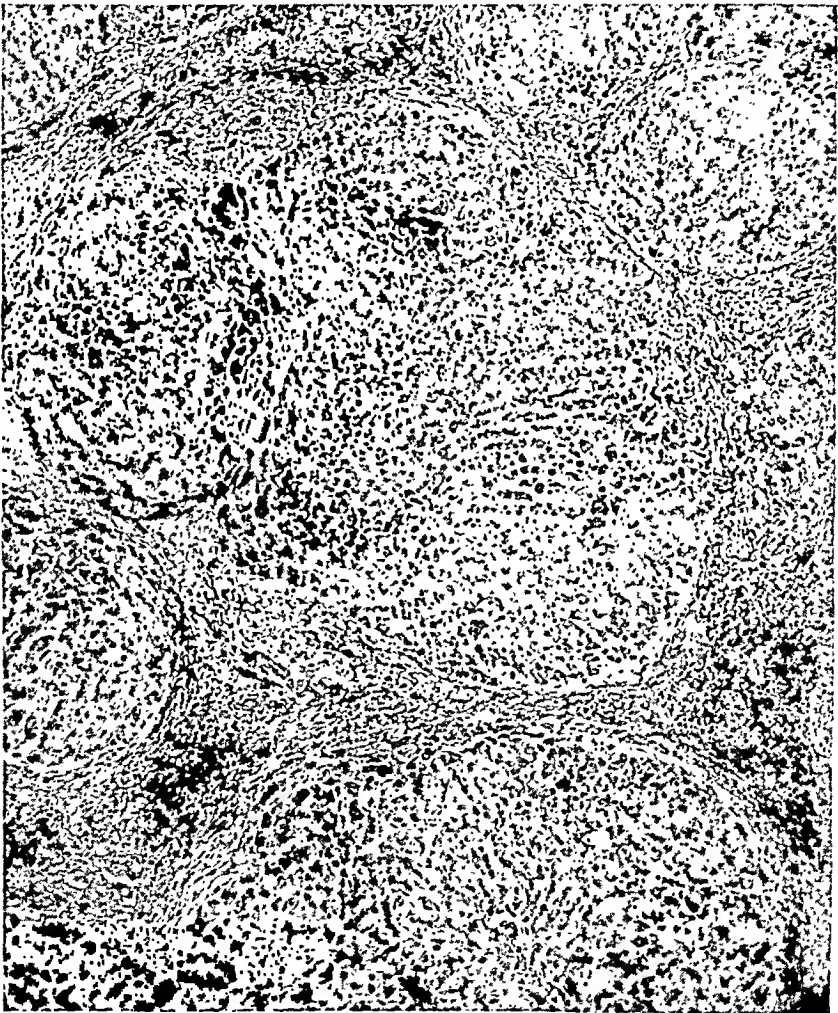


FIG. 1. Hemochromatosis. Section of liver showing pigment deposits. (X 58)

enough, however, to continue his usual work as a millwright. Urine sugar and urinary frequency had been known to be present for an indefinite period of from one to five years. He had noted that the whites of his eyes had been yellow for about five years. For the past few summers his skin had tanned easily and deeply. There was no history of taking alcohol or of exposure to copper or other chemicals.

Examination: The temperature, pulse and respiration were normal. The patient seemed in a fair state of nutrition and did not appear ill. There was a pronounced dark yellow color to the conjunctivae, but there was no skin icterus nor any abnormal pigmentation of the mucous membranes. No abnormal skin pigment was noted except a slight amount of grayish discoloration of the forearms more marked distally. The heart and lungs appeared normal except for a systolic apical murmur. The liver was palpated a hand's breadth below the rib border and seemed very firm. The spleen edge was noted three fingers' distance below the rib margin. No peripheral edema was present. The nervous system revealed no abnormal findings. The blood pressure



FIG. 2. Hemochromatosis. Section of pancreas showing pigment deposits. ($\times 110$)

was 130 systolic and 60 diastolic. The blood Wassermann and flocculation tests were negative. The urine gave a three plus sugar test and was otherwise normal.

Course: Because of the apparent diabetes, insulin and dietary therapy were prescribed on January 15, 1937. Three days later fever and cough developed and the patient was confined to bed. The temperature became normal after four days, but drowsiness, anorexia and weakness were marked and persisted. Despite the taking of 30 units of insulin daily glycosuria continued, but no ketonuria was present. The blood sugar on January 23 was 306 mg. per cent. Examination revealed a slight degree of skin icterus, and scattered râles were heard throughout both lungs. In the early morning of January 26 he had a large black stool and soon thereafter a large emesis of apparent old blood. Afterwards weakness was more marked and he was hospitalized in the late afternoon of January 26. The temperature was 99.4° F., the pulse 84, and the respirations 20. Examination revealed slight cyanosis but definite signs of pulmonary consolidation were lacking. The radials were thickened. The urine specimens contained sugar 1-5 plus but were otherwise not remarkable. On

January 26 the hemoglobin was found to be 80 per cent, the red blood cells 3,900,000, the white blood cells 8,800, polymorphonuclear leukocytes 65 per cent, lymphocytes 35 per cent. The red blood cells did not appear abnormal. The blood non-protein nitrogen was 50 mg. per cent, the blood sugar 357 mg. per cent, the icterus index 14 and the carbon dioxide combining power 58 volumes per cent. On January 27 the non-protein nitrogen was 47 mg. per cent. During his hospital stay insulin was given and because very little food or fluid was taken by mouth dextrose and normal saline were given parenterally. The temperature varied between 99–100° F., the pulse between 80–110, the respirations between 20–34. The blood pressure was 130 systolic and 70 diastolic. Drowsiness progressed to stupor and a state of shock gradually developed. No urine was passed after 9 a.m. on January 27. Pulmonary edema developed, and the patient

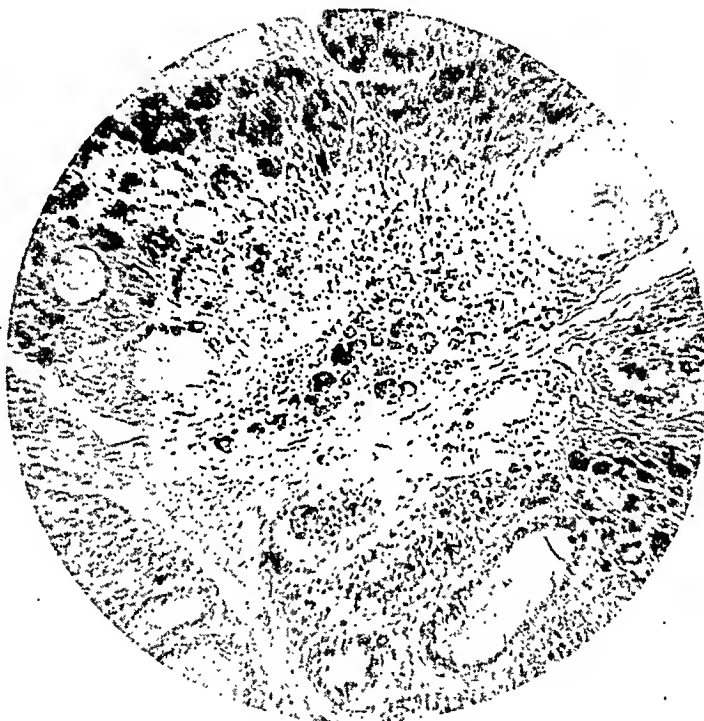


FIG. 3. Hemochromatosis. Section of thyroid showing pigment deposits. ($\times 110$)

died at 5 p.m., 28 hours after entry to the hospital and 10 days after having first been seen by the author. The presence of hemochromatosis as a primary diagnosis was suspected.

Autopsy was performed three hours post mortem by Dr. T. C. Wyatt. There was a slight yellowish tinge to the skin and mucous membranes, no edema. The peritoneal cavity contained 750–1000 c.c. of fluid. The bowel felt doughy, and the bowel and stomach contained considerable old blood. The liver weighed 2060 gm.; its edge extended 4–6 cm. below the ribs. The capsule was 2–10 mm. thick; the surface was rough and finely nodular. The gall-bladder was unusually dilated (8–10 cm.) and contained many small granular masses. Lymph nodes around portal vein and common bile duct were reddish brown in color; the mesenteric nodes were of the same color, but some were grayish in color. The pancreas was small, yellow brown in color. The spleen weighed 485 gm., and was enlarged and bound by dense grayish

adhesions to the diaphragm and ribs. Its capsule was 4–5 mm. thick; the cut surface was grayish red, without brown pigment. Each pleural cavity contained 500–700 c.c. of fluid. The mediastinum and pericardium were normal. The bronchi were red in color. Heart weight was 345 gm.; the myocardium was brownish in color. The aortic and mitral valves were thickened. The aorta showed marked sclerosis, numerous elevated yellow-gray and reddish areas. The esophagus, 8–10 cm. from upper end, showed marked dilatation of veins, some 1 cm. in diameter, and this condition extended to cardia. The lower ileum and colon contained black tarry material. The kidneys weighed 175–180 gm. There was no brown pigment in either kidneys or adrenals. Pelvis was negative.

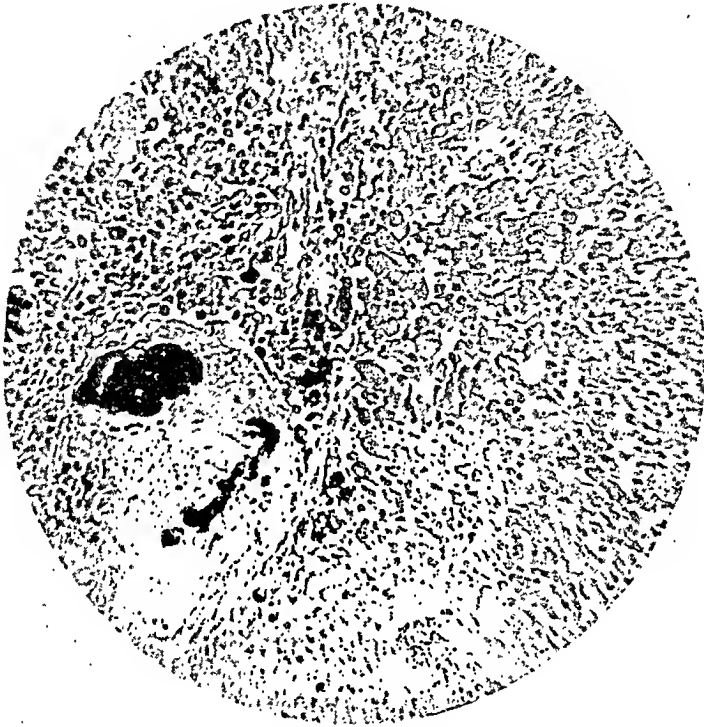


FIG. 4. Hemochromatosis. Section of abdominal lymph node showing pigment deposits. ($\times 175$)

Microscopic examination: Heart: Some slight evidence of focal degeneration in muscle cells with fibrosis. Lungs: Some acute bronchopneumonia. Scattered masses of dense fibrin in alveoli, also numerous mononuclear and multinuclear cells of phagocytic type some of which contain yellow brown pigment. Areas of hemorrhage. Spleen: Some diffuse fibrosis. Marked chronic fibrous perisplenitis. Some perivascular connective tissue thickening with degeneration and calcification. There is relatively little evidence of pigmentation in the sections. Liver: (Figure 1) Diffuse periportal cirrhosis with considerable brownish pigment largely in phagocytes in connective tissue and bile ducts. There is also some pigmentation of bile duct epithelium. There is marked proliferation of bile ducts in bands of connective tissue which lie between liver lobules. There is relatively little evidence of active necrosis of liver cells. There is chronic fibrous perihepatitis. Kidneys: Throughout the cortex are rare areas of fibrosis and degeneration involving glomeruli and tubules such as are seen in arteriosclerotic nephritis. There is almost no pigmentation. Adrenals:

Some pigmentation in zona glomerulosa and cortex without active necrosis or evidence of fibrosis. Pancreas: (Figure 2) Considerable widespread fibrosis tending to be interalveolar as well as interlobular. Considerable pigment in the connective tissue septa and to a lesser extent in the alveolar epithelium. There is no evidence of active necrosis or inflammatory reaction, all changes found are chronic. Islands of Langerhans are difficult to identify, but a few are seen imbedded in connective tissue. Thyroid: (Figure 3) Rather extensive pigmentation of alveolar epithelium with active degeneration of epithelium and diffuse fibrosis. Considerable pigment in phagocytes. Lymph Nodes: (Figure 4) Marked pigmentation in mononuclear and multinuclear phagocytes. Giant cells are grouped in places to form tubercle-like lesions. Certain giant cells enclose dense hematoxylin stained non-cellular material resembling calcium salts. Bone Marrow: Active leukoblastic and erythroblastic activity. There seems to be some scarcity of mature polymorphonuclear cells. Megakaryocytes are numerous. Aorta: Considerable thickening and degeneration of intima with some extension into media. No evidence of active inflammatory reaction, some calcification. Bronchus: No definite evidence of inflammatory reaction in wall. Pigmentation of tissues just outside bronchus.

Sections of liver, pancreas and thyroid were stained with potassium ferrocyanide and counterstained with eosin and showed the granular pigment described above to be iron-containing.

Diagnosis: Hemochromatosis. Cirrhosis of liver with brown pigment. Splenomegaly with marked chronic perisplenitis. Dilated veins in mucous membrane of esophagus with probable rupture. Hypostatic congestion of lungs with some bronchopneumonia. Rather marked arteriosclerosis. Pigmentation of myocardium. Bilateral hydrothorax. Hydroperitoneum.

DISCUSSION

A case of hemochromatosis in a middle aged man is reported with autopsy findings. The noteworthy features of this case are: (1) the presence of little or no skin pigment; (2) the deep yellowish brown pigmentation of the conjunctivae of long duration; and (3) the unusually large esophageal varices, rupture of one being the apparent cause of death. The absence of skin pigmentation may have been due to the fact that the disease was not fully developed although some of the symptoms had been present for five years. The lack of adrenal involvement in this case may explain the absence of melanin pigmentation. Sheldon³ in his review of the literature of hemochromatosis found absence of skin pigment in 16 per cent of the cases when skin pigmentation was mentioned. He found pigmentation of the forearms, as in this patient, mentioned 25 times. The deep yellowish brown pigmentation of the conjunctivae noted in this case apparently is not common, being noted in Sheldon's review only nine times. The damage to the portal circulation, resulting in marked esophageal varices rupture of one being the apparent cause of death, is the outstanding feature of the author's case. Several of the dilated veins were 1 cm. in diameter. Sheldon found in the cases reported in the literature that hematemesis was mentioned but six times in five of which it was fatal, and that it accounted for 5 per cent of the deaths from this disease. He comments on hematemesis as a cause of death in hemochromatosis, stating that it is a rarity, and that death usually occurs from some other cause before the liver has become appreciably shrunken. The response to insulin in this patient was not good, yet insufficient time was available to appraise its action. There is a prevalent belief that the diabetes associated with hemochromato-

sis is insulin resistant. However, Sheldon found that in 70 per cent of the cases in which it was used its action was satisfactory. As is usually the case the etiology was not apparent in this patient. No exposure to alcohol, copper or other chemicals was present.

REFERENCES

1. BLANTON, W. B., and HEALY, W.: Hemochromatosis, Arch. Int. Med., 1921, xxvii, 406-420.
2. BUTT, H. R., and WILDER, W. M.: Hemochromatosis: A report of thirty cases diagnosed during life, Proc. Staff Meet. Mayo Clin., 1937, xii, 625-627.
3. SHELDON, J. H.: Hemochromatosis, Humphrey Milford, 1935, Oxford University Press, London.

COMPLETE AURICULOVENTRICULAR BLOCK FOLLOWING CORONARY OCCLUSION; A CASE REPORT*

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COMPLETE heart-block as a result of acute coronary thrombosis is a relatively uncommon condition. Numerous investigators have reported occasional cases of complete heart-block so that we may arrive at a fair estimate of its occurrence in all cases of heart disease. White¹ quotes Allan, 1928, stating that coronary sclerosis is common and that of 1000 consecutive autopsies, 371 (37.1 per cent) showed coronary sclerosis. Of these, 238 (64 per cent) showed myocardial damage with fatty changes in 48 and fibrosis in 190. White¹ also quotes Barnes and Ball, 1932, who found in 49 cases of myocardial infarction following coronary thrombosis that the anterior descending branch of the left coronary was involved in 28 cases, the right coronary in 20 cases, and the circumflex branch of the left coronary in 17 cases. In these cases the infarcted areas involved the apex and anterior portion of the ventricle in 25, the posterior basal portion of the left ventricle in 21, and a combination of both in three. Saphir et al.¹ noted the involvement of both coronaries in 34 cases. Sprague and Orgain¹ in 3889 autopsies found only 131 with some degree of coronary occlusion. In 61 cases of acute coronary thrombosis the occlusion was limited to one coronary in only 17 instances. In 46 of their cases the left coronary was involved and in 21 the right coronary.

Complete heart-block following acute coronary thrombosis was reported by Stengel,² 1905. Willius,³ in 1926, reported two cases and stated that the condition had been seen only twice up to 1926 in the Mayo Clinic. Sigler,⁴ in 1927, reported a case with electrocardiographic evidence of a right coronary occlusion. Other instances of this condition have been reported by Geraudel et al.,⁵ Geraudel and Lereboullet,⁷ Frothingham, Nuchard, and by Parsonnet and Parent.⁸

Smith,⁶ in 1930, stated that Levine and Brown had observed two cases of complete auriculoventricular block in a series of 145 cases of coronary thrombosis,

* Received for publication July 11, 1938.

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and that Parkinson and Brown in a series of 100 cases of coronary occlusion had noted one case of this type of block.

In a review by Ball⁹ 16 cases of this nature are discussed. Individual cases reported by Neuhof and by Carter and McEachern were included. Ball found that the right coronary was involved in 93 per cent and the left coronary in 7 per cent. Schwartz stated that in all cases of coronary thrombosis with complete heart-block the artery to the posterior wall and the auriculoventricular node must be involved.

Salcedo-Salgar and White,¹⁰ in a careful study of the relations of various forms of heart-block to coronary disease, found that in a series of 328 cases of coronary thrombosis the incidence of auriculoventricular block was 4.2 per cent.

With the foregoing résumé in mind we present the following case.

CASE REPORT

Case History. The patient, C. R., white male, aged 56 years, was admitted to Touro Infirmary, March 22, 1937, at 5 a.m., in a stuporous condition. The history was obtained from his wife and family physician. The chief complaint was precordial pain. Four days previous to admission, the patient consulted his physician complaining of "gas on the stomach." His blood pressure was 130 systolic and 70 diastolic; there was no abdominal distention. The following morning he suffered severe precordial pain radiating to the shoulder and down both arms to the fingers. He was very restless and his respirations were somewhat rapid and labored. The pain was so severe that $\frac{1}{4}$ grain of morphine was given; this was repeated in a half hour, with some relief. His temperature was 99° F. the night before admission. The patient had had a similar attack 25 years previously. He gave no history of venereal disease.

Physical Examination. Blood pressure was 60 systolic and 40 diastolic; pulse 70 and irregular. The pupils were contracted. Breathing was rapid and irregular. The tongue was coated; head, neck, lungs and abdomen were negative. The heart sounds were distant and irregular; no murmurs were heard. There was slight cyanosis of the finger nails.

Course. An electrocardiogram was taken on admission (figure 1), revealing complete heart-block. Caffeine sodium benzoate gr. $7\frac{1}{2}$ and morphia gr. $\frac{1}{4}$ were given one hour later. At 9:30 a.m., the patient became cyanotic and was cold and clammy. Pulse was not felt, heart beat could not be heard. Temperature was 102° F. The patient died five hours after admission.

Postmortem Examination. Gross examination of the heart and pericardium: The pericardium contained 30 c.c. of clear, straw-colored fluid. There were no adhesions nor exudate present. Beneath the epicardium on the surface of the heart were noted many small areas of hemorrhage which were most numerous over the left ventricle, including the entire apex. No emboli were found in the pulmonary artery. The heart was removed and sectioned. None of the valvular areas showed abnormalities other than dilatation of the atrio-ventricular rings. All chambers of the heart were markedly dilated. The left ventricular muscle was narrowed and presented a necrotic zone near the apex. Here a small amount of thrombosis was noted within the heart muscle and between the fenestration within the lumen of the left ventricle. The entire wall of the left ventricle presented numerous small and a few larger petechial hemorrhages. Many mural thrombi were present between the muscle fibers. The right ventricular muscle was also markedly dilated. The ostiae of the coronary arteries were patent. Marked sclerosis was noted which was most marked in the left coronary artery especially in the descending branch. In probing the coronary artery, a thrombus was encountered 1 cm. from the ostium of the left coronary. Below this

the anterior descending branch was completely thrombosed. There was infarction with recent hemorrhage of the interventricular septum. The heart weighed 375 grams.

Lungs: The right lung measured 22 cm. in length by 15 cm. in width and $4\frac{1}{2}$ cm. in thickness. The external surface was smooth and glistening and presented several small calcified tubercles scattered over both the apex and base. A considerable amount of anthracotic pigment was present. No areas of consolidation were noted. The lung sectioned with no increased resistance. The posterior surface at the base presented a mottled color, and oozed a considerable amount of blood. No dilatation of the bronchi or bronchioles was noted. No areas of infarction were noted. The remainder of the lung was normally crepitant. The right lung weighed 325 grams.

The left lung measured 20 cm. in length by 11 cm. in width and 4 cm. in thickness. The base of the left lung was considerably less crepitant than normal, but no

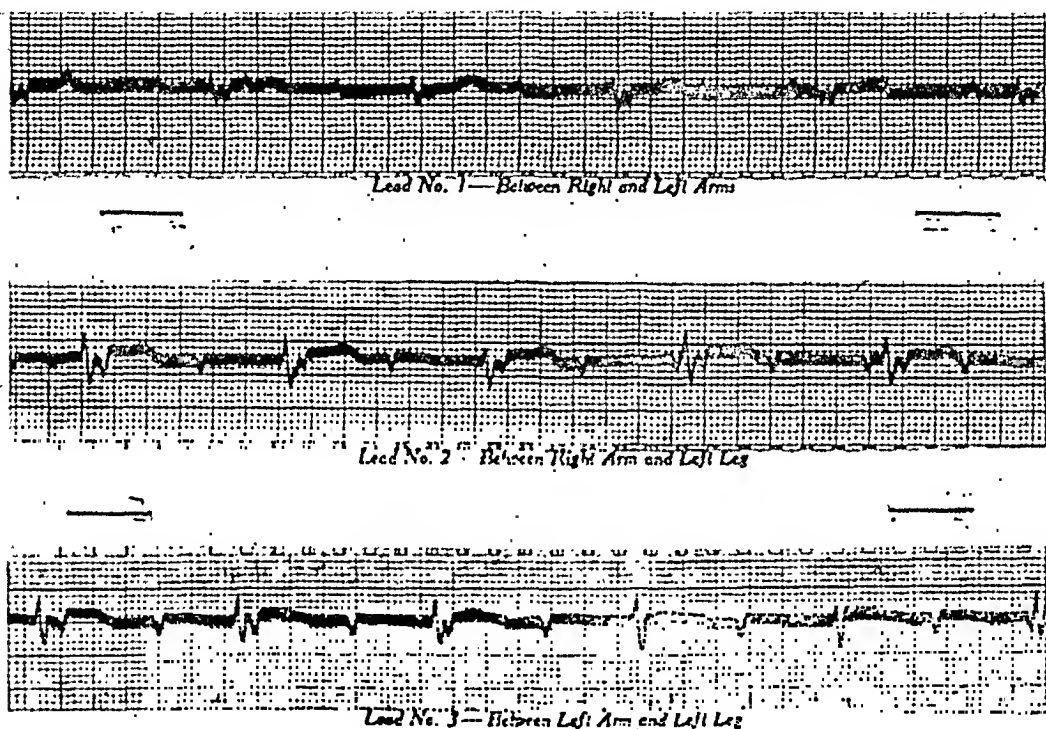


FIG. 1. Electrocardiogram revealing left axis deviation, auricular rate of 80, ventricular rate of 55, definite myocardial disease with complete atrioventricular block and intraventricular delay.

definite areas of consolidation were noted. Upon sectioning, the posterior inferior surface of the lung was darker red than normal and the remainder of the lung was pink. In these darker areas considerable oozing of the blood was noted. The left lung weighed 270 grams.

Liver: The liver measured 20 cm. in length by 25 cm. in width and $9\frac{1}{2}$ cm. in thickness. The outer surface presented numerous small petechial hemorrhages beneath Glisson's capsule. The outer surface was smooth. The liver sectioned without resistance. The cut surface was a mottling of many colors. Numerous small areas of hemorrhage were noted. The liver was markedly congested; all of the venous radicles were dilated. A considerable amount of yellowish discoloration was noted on the cut surface. The liver weighed 1900 grams.

Anatomical Diagnoses. 1. Coronary thrombosis with infarction—entire left coronary artery. 2. Coronary arteriosclerosis. 3. Acute dilatation of the heart and



FIG. 2. Section through the interventricular septum showing a portion of the large mural thrombus, MT, attached to endocardium overlying the swollen and edematous bundle of His, H. ($\times 943$)

mural thrombi. 4. Congestion of liver, spleen and kidneys. 5. Atelectasis. 6. Healed pulmonary tuberculosis. 7. Hypostatic pneumonia.

Microscopic Findings. Lungs: There was marked chronic passive congestion

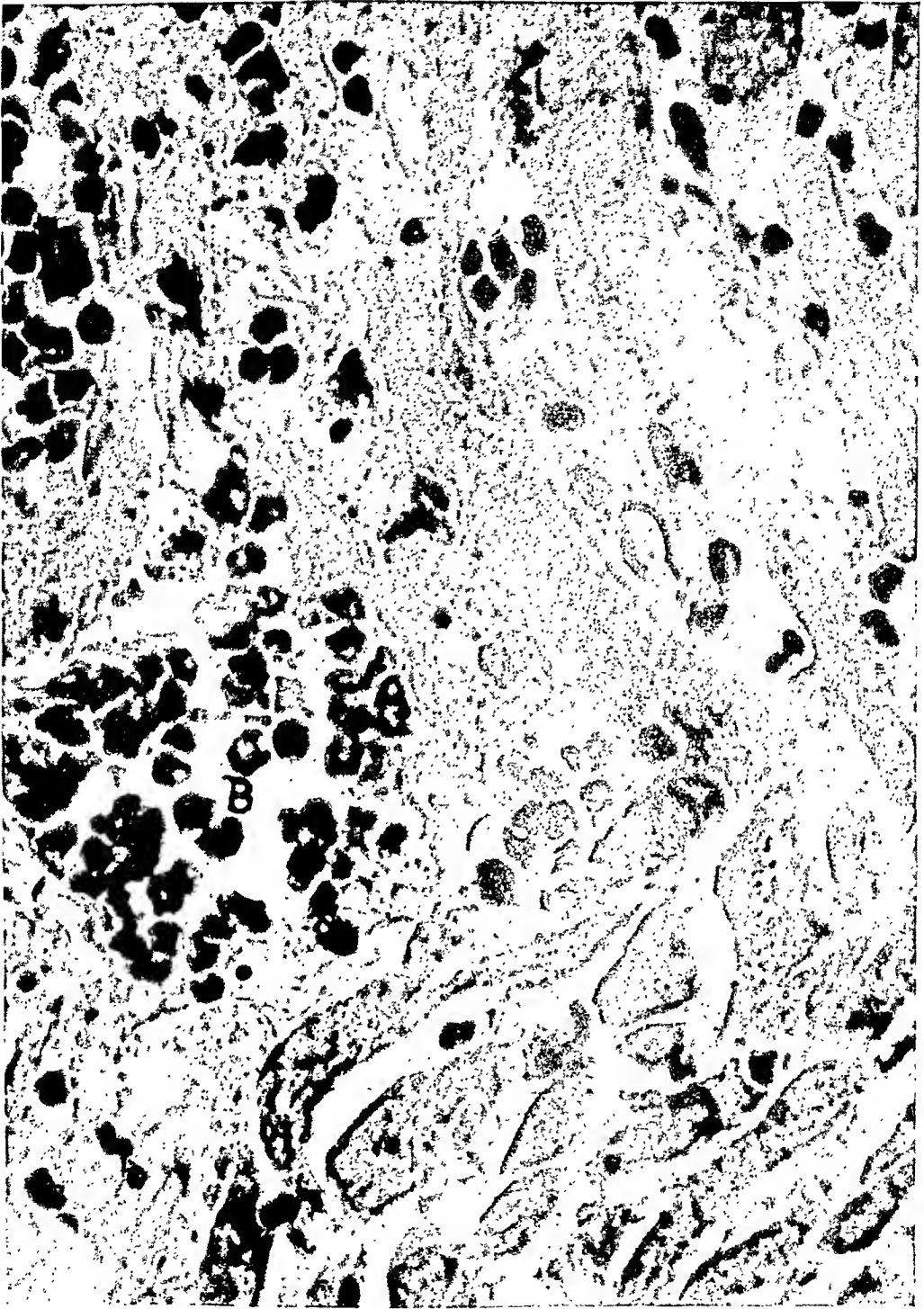


FIG. 3. Section through the interventricular septum showing evidence of a recent hemorrhage, *B*, with interstitial edema and beginning necrosis of muscle fibers. ($\times 943$)

with central necrosis and fatty degeneration. Only a thin rim of hepatic cells around the capsule were functioning and many of them showed varying degrees of degeneration with pyknotic nuclei. There was increase in connective tissue around the portal spaces.

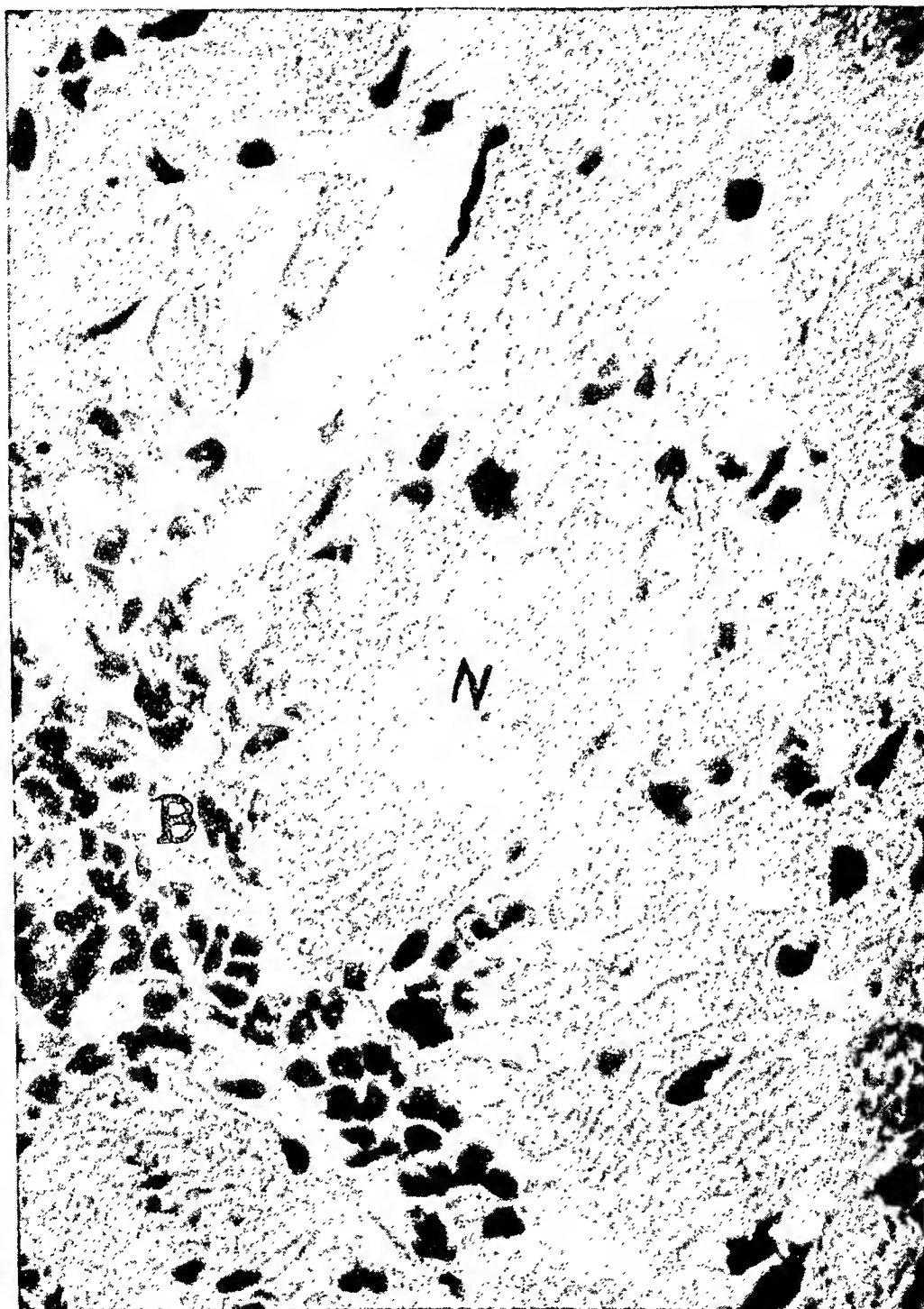


FIG. 4. Section through the interventricular septum showing a recent hemorrhage into the conduction system, *B*, with the necrosis involving the conduction system, *N*. ($\times 943$)

Heart: There were left ventricular areas of necrosis with widespread degenerative changes in the musculature generally, and also many areas of scarring in various stages of development.

Figure 2 demonstrates a mural thrombus attached to the interventricular septum with edema of the bundle of His. Figure 3 shows a recent hemorrhage into the septum with edema and beginning necrosis of muscle fibers. Figure 4 shows the hemorrhage into the conduction system with necrosis.

DISCUSSION

From the history, physical examination and electrocardiogram there is little doubt as to the clinical presence of coronary thrombosis and complete heart-block. The autopsy findings are sufficient to prove a thrombosis of the entire anterior descending branch of the left coronary.

As has been frequently shown, the left coronary artery is more frequently involved in thrombosis than the right, but this is not the usual site of acute coronary thrombosis in cases with complete heart-block. The usual condition as stated by Ball⁹ is that the right coronary is affected in 93 per cent and left coronary in 7 per cent of such cases.

Schwartz¹¹ states that "no matter which artery supplies the posterior wall of the left ventricle, heart-block invariably results from a closure posteriorly." This of course is in accordance with the blood supply to the auriculoventricular node, concerning which Gross states that the right coronary supplies it in 92 per cent of all cases and the left coronary in 8 per cent. Levine reports a case of block with thrombosis of the left anterior descending artery. Rothschild's case, mentioned by Ball,⁹ was one in which the electrocardiogram was a T_3 type originally with apparent recovery, followed by another attack and death, with the electrocardiogram a T_1 type.

We have described numerous small mural thrombi in the ventricle of this case and have shown a section of a larger one on the interventricular septum with hemorrhage into the upper part of the septum, and with edema and necrosis involving the conduction system.

From the patient's history, it is not our impression that complete auriculoventricular block existed prior to the fatal attack, as no signs or symptoms of this condition were manifested. However there was a history of a similar attack 25 years before, at which time he was 31 years old. On the whole, therefore, it is unlikely, but not impossible, that previous block had existed.

The fairly numerous scars in the myocardium associated with marked sclerosis of both coronaries, with the left more markedly involved, made the patient a good candidate for heart-block. Whether any degree of heart-block existed, either partial or transient, we cannot say, but we feel reasonably sure that he had never been sufficiently ill to request medical advice and had lived a normal active life. It is certain that the left coronary artery was completely thrombosed with infarction of the interventricular septum and that the blood supply to the auriculoventricular node was not acutely disturbed. In this respect our case is similar to two cases of ischemia and necrosis of the auriculoventricular bundle as reported by Yater, Cornell and Claytor.¹² Jellick, Cooper and Ophuls,⁹ 1906, also reported a case of ischemic necrosis of the bundle of His.

SUMMARY

1. A case of complete thrombosis of the left coronary artery 1 centimeter from its origin, with infarction of the apex of the heart and interventricular

septum with hemorrhage into and necrosis of the septum associated with complete auriculoventricular block, resulting in death, is herewith presented.

2. A brief summary of the association of coronary disease with complete heart-block is given.

3. The review of recent work as well as the pathologic findings in this case indicate that the pathogenesis of complete heart-block in coronary thrombosis is not the same in all instances.

We wish to express our appreciation to Dr. J. A. Lanford, of Touro Infirmary, for the autopsy protocol; to Dr. Emmerich von Haam, of the Department of Pathology, Ohio State University Medical School, for the microscopic sections; and to Dr. J. R. Schenken, of the Department of Pathology, Louisiana State University School of Medicine, for aid in the study and for microphotographs of sections of heart specimen.

BIBLIOGRAPHY

1. WHITE, P. D.: Heart disease, 2nd ed., 1937, The Macmillan Company, New York, 344.
2. STENGEL, A.: A fatal case of Stokes-Adams disease with autopsy showing involvement of bundle of His, *Am. Jr. Med. Sci.*, 1905, cxxx, 1088-1091.
3. WILLIUS, F. A.: Infarction of the interventricular septum with complete heart-block and Stokes-Adams seizures, *Med. Clin. N. Am.*, 1928, x, 601-604.
4. SIGLER, L. H.: Case of coronary occlusion with complete heart block, *ANN. INT. MED.*; 1927, i, 835-842.
5. GERAUDEL, E., BRODIN, P. L., and LEREBoulLET, J.: Fatal case of Adams-Stokes syndrome due to necrosis of auriculoventricular bundle with stenosis of coronary artery, *Arch. d. mal. du coeur*, 1929, xxii, 1-15.
6. SMITH, K. S.: Coronary thrombosis and complete heart-block, *Lancet*, 1930, i, 685-687.
7. GERAUDEL, E., and LEREBoulLET, J.: Adams-Stokes syndrome developing rapidly from coronary thrombosis and thrombosis of artery of bundle of His; electrocardiographic study, *Paris méd.*, 1930, ii, 25-29.
8. PARSONNET, A. E., and PARENT, S.: Auricular flutter with complete auriculoventricular block in patient with coronary disease, *Arch. Int. Med.*, 1933, li, 938-946.
9. BALL, D.: The occurrence of heart-block in coronary artery thrombosis, *Am. Heart Jr.*, 1933, viii, 327.
10. SALCEDO-SALGAR, J., and WHITE, P. D.: Relationship of auriculoventricular and intra-ventricular block to clinical manifestations of coronary disease, angina pectoris and coronary thrombosis, *Am. Heart Jr.*, 1935, x, 1067-1079.
11. SCHWARTZ, S. P.: Auriculoventricular dissociation and the Adams-Stokes syndrome in acute coronary vessel closure, *Am. Heart Jr.*, 1936, xi, 554.
12. YATER, W. M., CORNELL, V. H., and CLAYTOR, T.: Heart-block due to bilateral bundle branch lesions, *Arch. Int. Med.*, 1936, lvii, 132.

EDITORIAL

RECENT OBSERVATIONS ON PLEUROPNEUMONIA-LIKE ORGANISMS

Recent investigations have aroused great interest among bacteriologists in the so-called pleuropneumonia group of organisms. Study of this group has been relatively neglected, partly because of technical difficulties in maintaining cultures and partly because it has not been known to be important as a cause of disease in man.

The first known species of this group of organisms was isolated by Nocard in 1898 from the lungs and pleural exudates of cattle dying of pleuropneumonia. He first obtained his cultures by growing the organisms within collodion sacs inserted into the peritoneal cavity of rabbits. Later he obtained them also *in vitro* in serum broth. Bordet (1910) and Borrel et al. (1910) were the first to give adequate descriptions of the unusual morphology of these organisms. In 1923 Bridre¹ and Donatien isolated a related species from victims of the disease agalactia of sheep and goats. As neither of these species is pathogenic for man, these observations did not excite widespread medical interest.

Important contributions regarding the morphology of these organisms have been made more recently by Ledingham¹ and by his associate Klieneberger,² by the application of new technical methods. The principal viable forms in old cultures occur as fine granules which vary from $0.5\ \mu$ down to $0.2\ \mu$ or less in diameter. Under favorable conditions, from such granules slender threads grow out which may form a single filament, or they may bud out from several parts of the granule to form delicate star-shaped structures. These threads become branched and after a few days form a fairly dense mycelial-like network. Soon nodular swellings appear at various spots in the filaments, and gradually enlarge to contain fine and coarse granules and larger inclusions which take a reddish color with Giemsa's stain, in contrast with the pale bluish color of the background. Along the course of the threads isolated reddish staining granules also appear, apparently as a result of condensation of the cytoplasm. Particularly about the margin of the colonies the threads become enlarged to form coarse globular or club-shaped bodies. In the older colonies the threads become largely transformed into fine granules and fragments and the coarse yeast-like bodies.

The fine granules are filtrable, and hence the organisms have been regarded by some as related to the viruses. Unlike the latter, however, they will grow on artificial media free from living tissue cells, and in certain phases they resemble bacteria in appearance. In spite of this apparently complicated life cycle, Ledingham regards these as simple primitive organ-

¹ LEDINGHAM, J. C.: Growth phases of pleuropneumonia and agalactia on liquid and solid media, Jr. Path. and Bact., 1933, xxxvii, 393-410.

² KLIENEBERGER, E.: Colonial development of the organisms of pleuropneumonia and agalactia on serum agar and variations of the morphology under different conditions of growth, Jr. Path. and Bact., 1934, xxxix, 409.

isms and attributes their pleomorphism to their extreme plasticity rather than to a fundamentally complicated structure.

In order to secure a wider range of material for the study of this group, Klieneberger³ instituted a systematic search for other species and reported finding two: one in symbiosis with a streptococcus isolated from a guinea pig, and a second in symbiosis with *Streptobacillus moniliformis*.

This latter organism had already attained some significance in human medicine. It was first isolated by Schottmüller (1914) from the blood of a human case of rat bite fever, and reported as *Streptothrix muris rattii*.^{*} Blake (1916) obtained the same organism from the blood during life and post mortem from the endocardial vegetations of a case of rat bite fever. In 1925 Levaditi isolated a similar organism from a sporadic case of rat bite fever, and gave it the name *Streptobacillus moniliformis*. He and his associates showed that it is a common harmless saprophyte in the nasopharynx of normal rats.

In 1926 Parker and Hudson⁴ described as *Haverhillia multiformis* what was undoubtedly the same organism. This they obtained from the blood of 11 of 21 cases of an acute epidemic infectious disease which they termed Haverhill fever, or erythema arthriticum epidemicum. This outbreak was characterized clinically by an acute onset with fever, malaise, vomiting, headache, a blotchy morbilliform eruption and an acute, often severe, polyarthritis. This epidemic was not caused by rat bites, but on epidemiological grounds was thought to be milk borne. None of these investigators noted pleuropneumonia-like organisms in their cultures, but they were almost certainly present.

Klieneberger obtained a number of other strains of *Streptobacillus moniliformis* by inoculating mice with the pharyngeal exudate of rats, and found pleuropneumonia-like organisms in all. By special methods she was able to separate the latter from the *S. moniliformis* in pure culture, and has carried the cultures for several years without reversion to the *S. moniliformis* type. No one as yet, however, has obtained the latter free from pleuropneumonia-like organisms. All the strains of the latter isolated from *S. moniliformis* cultures were antigenically identical, but distinct from the cultures from pleuropneumonia and agalactia. She reported examining many other stock cultures of various bacteria without finding other instances of symbiosis. She was able, however, to induce symbiosis of the pleuropneumonia-like organism with *Clostridium tetani* and with *Cl. tetanomorphum*, each organism growing more luxuriantly than in pure culture.

These observations as to the symbiosis of pleuropneumonia-like organisms with *S. moniliformis* have been completely confirmed by Dienes and

³ KLIENEGER, E.: The natural occurrence of pleuropneumonia-like organisms in apparent symbiosis with *Streptobacillus moniliformis* and other bacteria, Jr. Path. and Bact., 1935, xl, 93-105.

^{*} This disease is entirely distinct from the rat bite fever caused by *Leptospira morsumuris* (*Spirillum minus*).

⁴ PARKER, F., and HUDSON, N. R.: The etiology of Haverhill fever (erythema arthriticum epidemicum), Am. Jr. Path., 1926, ii, 357-379.

Edsall.⁵ They also cultivated similar organisms from the middle ear of a rat with "rolling disease," and from a Bartholin gland abscess of a laboratory worker who had been in contact with rats (unmixed with *S. moniliformis*).

Klieneberger⁶ has isolated similar but antigenically distinct strains from pneumonic lesions or abscesses in rats' lungs. She cultivated another strain from suspensions containing Woglom's pyogenic agent of rats, which had been regarded as probably a filtrable virus.⁷ Findlay, Klieneberger et al.⁸ isolated other strains from the brains of mice which had been inoculated with neurotropic yellow fever virus, and with lymphocytic choriomeningitis virus. These mice would become ill prematurely, and a portion of them would carry out spasmodically repeated rotary movements about their tails as an axis, hence the term "rolling disease." They recognized the similarity of the symptoms shown by these mice to those reported by Sabin in certain mice infected with toxoplasma, and they cultivated organisms antigenically identical with their own from Sabin's material. Sabin⁹ confirmed this, and reported cultivating similar organisms from the brain of one normal mouse, out of a large number examined.

More recently these investigators¹⁰ cultivated another strain from the joint tissues of rats suffering from a type of polyarthritis. They could reproduce the disease in mice by injecting into the foot pads filtered or unfiltered suspensions of joint tissue, or cultures grown from them, along with a bit of agar. Incidentally they confirmed Collier's observation that gold salts, such as solgenol B, had a marked protective effect in preventing experimental polyarthritis in rats, but sulfonamide compounds were ineffective.

They report detailed comparative studies of these different strains. They have obtained at least five strains which are antigenically distinct from each other and from pleuropneumonia and agalactia, as shown by agglutination and immunization tests. Morphologically they are similar, but minor differences can be distinguished in certain instances. They are pathogenic in varying degree for mice, less so for rabbits and rats, whereas guinea pigs are resistant. Several of the strains will produce arthritis in mice or rats, but not all do so readily. Animals which recover possess a high degree of immunity to reinfection with the same antigenic type. When detectable in tissues or exudates they usually appear as fine granules, short filaments or ring-like structures.

⁵ DIENES, L., and EDSALL, G.: Observations on the L-organism of Klieneberger, Proc. Soc. Exper. Biol. and Med., 1937, xxxvi, 740-744.

⁶ KLIENEBERGER, E., and STEABBEN, D. B.: On a pleuropneumonia-like organism in lung lesions of rats, with notes on the clinical and pathological features of the underlying condition, Jr. Hyg., 1937, xxxvii, 143.

⁷ KLIENEBERGER, E.: Studies on pleuropneumonia-like organisms: the L₁ organism as the cause of Woglom's "pyogenic virus," Jr. Hyg., 1939, xxxix, 260-265.

⁸ FINDLAY, G. M., et al.: Rolling Disease: New syndrome in mice associated with a pleuropneumonia-like organism, Lancet, 1938, ii, 1511-1513.

⁹ SABIN, A. B.: Isolation of a filtrable transmissible agent with "neurolytic" properties from toxoplasma-infected tissue, Science, 1938, lxxxviii, 189-190. Also *ibid.*, 575-576.

¹⁰ FINDLAY, G. M., et al.: The etiology of polyarthritis in the rat, Lancet, 1939, ii, 7-10.

Saprophytic strains belonging to this group have been isolated from the soil, sewage, etc., by Laidlaw and others (1936).

Sabin¹¹ has also produced a chronic arthritis in mice by intravenous or intraperitoneal injections of cultures of the strain he isolated from the brain of a normal mouse. He described this as a progressive proliferative polyarthritis resembling rheumatoid arthritis in man. There occurred fusiform swelling of the digits, proliferation of the synovial membrane, of the joint capsule, of the perichondrium of the articular cartilages, and of the connective tissue and probably endosteum of the epiphyseal marrow below the cartilage. The process often goes on to ankylosis of one or more joints. He was able to recover the organism in cultures from the joints as much as 70 days after inoculation by "blind passages," that is, by a series of subcultures repeated at short intervals without waiting for evidence of growth to appear.

Finally Swift and Brown¹² have reported the finding of pleuropneumonia-like organisms in the joint fluids of human cases of acute rheumatic fever. This was accomplished first by cultivation on the chorioallantoic membrane of chicks by frequent serial passages. After about five passages characteristic lesions appeared which were not obtained with exudates from other sources and from which pleuropneumonia-like organisms were cultivated on suitable media. Second, by intranasal inoculation of mice with exudate or with suspensions of inoculated chorioallantoic membranes they produced a pneumonia free from ordinary bacteria, from which directly or after filtration they could produce the characteristic lesions on chorioallantoic membranes, and recover pleuropneumonia-like organisms by direct culture. They also succeeded in cultivating the organisms directly from the joint fluid of one child with rheumatic fever and from an erythema nodosum nodule of a second case. Using three such cultures, some of which had not been passed through animals, they produced iritis in rabbits by intravenous injections, and pneumonia in mice by intranasal instillation, even in the first animal of the series. In their article, which appears to be a preliminary report of work in progress, they do not report the production of arthritis with these strains.

These observations indicate that pleuropneumonia-like organisms are much more common and widely distributed than has been realized. They are obviously important pathogenic agents for certain rodents as well as for cattle, sheep and goats. These studies also open up interesting possibilities as to their significance in human infection. The resemblance of the polyarthritis of rats and mice to human rheumatoid arthritis is striking and the reported recovery of such organisms from the joints in acute rheumatic fever is most stimulating. This finding is somewhat surprising in view of the

¹¹ SABIN, A. B.: Experimental proliferative arthritis in mice produced by filtrable pleuropneumonia-like microorganisms, *Science*, 1939, lxxxix, 228-229.

¹² SWIFT, H. F., and BROWN, T. M.: Pathogenic pleuropneumonia-like microorganisms from acute rheumatic exudates and tissues, *Science*, 1939, lxxxix, 271-272.

immunity induced in animals by other species of this group. It is interesting, however, that arthritis was a prominent feature of Haverhill fever, and that it occurs in from 10 to 20 per cent of animals with agalactia.

As to the significance of these organisms as a cause of disease in man, the findings thus far reported can not be regarded as more than suggestive. They do call for extensive and careful investigations, not only in arthritis but in other obscure infections as well. The problem is a very complex one. The technical difficulties of cultivation are great. The possibility of contamination from outside sources seems hard to exclude. The occasional, even though rare occurrence of such organisms in apparently healthy individuals of the best experimental animal, the mouse, introduces an element of uncertainty into animal experiments and necessitates unusually careful and extensive controls. These difficulties should not be insurmountable, however, and with the problem mapped out and reasonably adequate experimental procedures available we may anticipate at least a rapid increase in our knowledge of this interesting group of organisms.

P. C.

REVIEWS

Pulmonary Tuberculosis in Adults and Children. By JAMES A. MILLER and ARVID WALLGREN. 198 pages; 19×25 cm. Thomas Nelson and Sons, New York. 1939. Price, \$3.50.

The book is a composite work by two men who are well known in their respective fields. They present essentially the same material in Nelson's "Loose-Leaf System of Medicine." The form of this book is similar to that used in Nelson's system.

The book is arranged in two sections, the first by Dr. Miller being that on pulmonary tuberculosis in the adult; the second by Dr. Wallgren covers tuberculosis in children. The subjects of both sections are systematically and relatively completely reviewed.

Dr. Miller introduces his subject by a discussion of the factors of resistance, immunity and allergy. The pages devoted to the evolution of pulmonary tuberculosis contain the author's concepts of the basic pattern of tuberculosis and these lead him to a new classification of pulmonary tuberculosis whereby he classifies tuberculosis into three basic forms, the non-phthisical, the pre-phthisical and the phthisical forms. The classifications are very good and incorporate into a definite schema certain forms which hitherto have escaped classification.

The clinical aspects of the disease are very well discussed and the descriptions are enhanced in value by some words on the clinicoroentgenological course of the disease. The last section is accompanied by some very clear roentgen-ray plates.

The rest of the section is devoted to discussion of diagnosis, differential diagnosis, treatment, complications and prevention of the disease. The part on treatment is complete in its scope, giving the various forms of treatment and some valuable information on each. It is not an exhaustive study but does give the pertinent facts. A bibliography completes the first section of the book.

Dr. Wallgren devotes the second section of the book to the disease in children.

There is an admirable discussion of allergy and immunity which is particularly valuable because one escapes the sense of confusion which so often accompanies this subject. The author believes that children who have successfully passed through a primary tuberculosis are to be regarded as a picked group who, when exposed to tuberculous infections, are in a more favorable position than uninfected children.

All the various tuberculin tests are described and their value discussed.

Tuberculosis in childhood is divided into primary, secondary and tertiary tuberculosis. The type arising from the first infection and resulting in the primary complex is termed primary tuberculosis. The disease that spreads directly from the primary infection is the secondary tuberculosis, and the late reinfection type is the tertiary. This is a somewhat different treatment than is usual in the discussion of this subject. Good roentgen-ray plates are presented in the discussion of the various types. The section is completed by a discussion of treatment and of prevention of childhood tuberculosis.

This book can be well recommended to those who are interested in pulmonary tuberculosis. Its completeness and its conciseness give it a special value. The classifications of the disease by Dr. Miller are a distinct advantage to our understanding of the subject. Dr. Wallgren gives a clear picture of the disease in childhood.

M. W. J.

Post-Mortem Appearances. By JOAN M. ROSS, M.D., B.S. (Lond.), M.R.C.S., L.R.C.P. 275 pages; 11×17 cm. Oxford University Press, New York, N. Y. 1939. Price, \$2.50.

This fourth edition shows some improvement over the preceding ones, especially the added chapter on "Diseases of the Blood-Forming Organs." In this new section, the essential findings are well given, without being controversial.

Some of the technics advocated differ from American customs, for instance, the employment of an opening incision beginning in the neck instead of the axilla. There is no mention of the chloride test for drowning. The book is extremely practical, thorough, and puts a needed emphasis on deaths from causes other than disease. For the student beginner in pathology, this book will simplify and make easier the digestion of the larger and more involved texts.

C. A.

Ophthalmology. By BURTON CHANCE, M.D. 240 pages; 11.5 × 17 cm. Paul B. Hoeber, Inc., New York. 1939. Price, \$2.00.

This pocket manual is one of a series on the history of medicine and consists of 26 chapters. The author has brought together in a compact form a concise review of the development of ophthalmology from the earliest time to the present era.

The classification of the material in some of the chapters appears somewhat confused and misleading, as in the case in Chapter IX, "Cataract in the Eighteenth Century," where the author devotes the first half to the subject but introduces various subjects in the second half; again in Chapter XXIII, "Modern British Contributors," the author inserts the activities of Julius Hirschberg of Berlin.

It would seem that in dealing with the development of diagnosis and treatment of glaucoma mention should have been made of the introduction of the tenometer with its great importance in accurately measuring the tension.

Under the head of "Treatment of Detachment of the Retina" in the chapter on "Ophthalmic Surgery," the author refers to the thermaphore of Sheehan of New York; undoubtedly he means to refer to Shahan of Saint Louis.

In spite of these criticisms and of minor errors, the volume is both entertaining and instructive. It is printed on paper of dull finish, in clear type, two factors which give added pleasure in any reading and which seem particularly important in a book on ophthalmology.

C. A. C.

Social Hygiene. By W. BAYARD LONG, M.D., attending Dermatologist, Director of Dermatology and Syphilis Clinics in St. Luke's Hospital, New York; and JACOB A. GOLDBERG, M.A., Ph.D., Secretary, Social Hygiene Committee, New York Tuberculosis and Health Association, and Social Hygiene Council of Greater New York. Cloth bound. 442 pages. 62 illustrations. Lea & Febiger, Philadelphia. 1938.

The authors have presented a collection of writings on the social aspects of the venereal diseases, dealing for the most part with the two which have most claimed the public eye in recent times, that is, syphilis and gonorrhea. These articles deal briefly with the diagnosis and treatment of the diseases and thoroughly with the social aspects and prevention.

The collection is admirably arranged so that the first series of articles deals mainly with the diagnosis and treatment while the latter group of articles deals more with prevention and methods of prevention. While syphilis and gonorrhea are the two venereal diseases which have received the foremost attention it can be seen by the methods suggested that they may be applied to the prevention of the other conditions as well. The article on the treatment of syphilis does not adhere strictly to the method or methods advocated by the Coöperative Clinical Group. The obstacles facing the methods of prevention are the lack of coöperation by the average general physician, and by the pseudo-pious attitude assumed by the average layman and social worker.

This book represents an excellent collection and would be well placed in the hands of any social worker engaged in handling these cases and in the hands of any physician who is treating these patients.

H. M. R., JR.

COLLEGE NEWS NOTES

GIFTS TO THE COLLEGE LIBRARY

Grateful acknowledgment is made of the receipt of the following donations to the College Library of publications by members:

Reprints

- Dr. Joseph H. Barach, F.A.C.P., Pittsburgh, Pa.—7 reprints;
Dr. John R. Cavanagh, F.A.C.P., Washington, D. C.—1 reprint;
Dr. Hervey M. Cleckley (Associate), Augusta, Ga.—1 reprint;
Dr. Jacob Gutman, F.A.C.P., Brooklyn, N. Y.—8th (Second Series), Supplement to "Modern Drug Encyclopedia and Therapeutic Guide"; also, 14 reprints;
Dr. Clifton K. Himmelsbach (Associate), Lexington, Ky.—8 reprints;
Dr. William E. Jahsman (Associate), Ferndale, Mich.—1 reprint;
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Dr. Wm. deB. MacNider, F.A.C.P., Chapel Hill, N. C.—4 reprints;
Dr. James R. Nakada, F.A.C.P., St. Louis, Mo.—2 reprints;
Dr. Oliver T. Osborne, F.A.C.P., New Haven, Conn.—1 reprint.
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Dr. William S. Middleton, F.A.C.P., Dean and Professor of Medicine of the University of Wisconsin Medical School, Madison, Wis., was the guest of honor at the 53rd annual dinner of the Association of ex-Resident and Resident Physicians of the Philadelphia General Hospital, held at the Bellevue-Stratford Hotel, Philadelphia, December 5.

Dr. Arthur C. Morgan, F.A.C.P., Philadelphia, as President of the Association, acted as Toastmaster.

The fifth annual down-state district meeting of the members of the American College of Physicians of Illinois was held on October 18 at Jacksonville, Ill. Luncheon was served at one o'clock at the Norbury Sanatorium, where the meeting was held in the afternoon. The following papers were presented by Fellows of the College:

- Dr. W. H. Newcomb, Jacksonville—"Pain in the Right Upper Quadrant"
Dr. Gerald M. Cline, Bloomington—"Reasons for Failure in the Management of Some Allergic Diseases"
Dr. Harold Swanberg, Quincy—"Errors in Roentgen Interpretation"
Dr. Thomas D. Masters, Springfield—"Management of Peripheral Vascular Diseases"
Dr. John R. Vonachen, Peoria—"Rocky Mountain Spotted Fever in Children"

A joint meeting was held in the evening with the Morgan County Medical Society, following a dinner at the Jacksonville Country Club. The guest speaker was Dr. James H. Means, F.A.C.P., Boston, Mass., ex-President of the College, who spoke on "Thyroid Disease."

Beginning September 1, 1939, Dr. Carlo J. Tripoli, F.A.C.P., New Orleans, La., was appointed Professor of Medicine in Charge of the Department of Medicine in the Graduate School of Medicine of the Louisiana State University Medical Center.

Dr. Andrew C. Woofter (Associate), Parkersburg, W. Va., has been appointed President of the Staff of the Camden-Clark Memorial Hospital, succeeding Dr. A. R. K. Matthews.

Dr. Arthur J. Logie (Associate), Director of the Division of Tuberculosis of the Florida State Board of Health, Jacksonville, Fla., was the guest speaker at the meeting of the Bay County Medical Society in Panama City, Fla., on October 17, and at the meeting of the Second Medical District in Quincy on October 19. Dr. Logie spoke on "More Recent Advances in Tuberculosis."

Fifty Fellows and Associates of the American College of Physicians residing in the State of Virginia attended the sectional meeting held at Richmond on October 4, in conjunction with the Medical Society of Virginia. Dr. Louis Hamman, F.A.C.P., Baltimore, Md., and Dr. Frank Hagner, New York City, were guest speakers.

The following officers were elected:

Dr. William B. Porter, F.A.C.P., Richmond, Chairman of the Virginia Section
Dr. Henry B. Mulholland, F.A.C.P., University, Vice Chairman
Dr. C. M. Caravati, F.A.C.P., Richmond, Secretary

It has been planned to hold one social and two scientific regional meetings each year.

On October 21, 1939, the Medical Advisory Board of the Austen Riggs Foundation held its annual meeting at Stockbridge, Mass., with between forty and fifty psychiatrists and internists in attendance. A paper discussing certain aspects of cases falling in the neurotic-psychotic borderline was read. The meeting was conducted by Dr. Austen Fox Riggs, F.A.C.P., Medical Director of the Foundation.

The following members of the College took part in the meeting:

Dr. Walter W. Palmer, F.A.C.P., New York City.
Dr. Lauren H. Smith, F.A.C.P., Philadelphia
Dr. William B. Terhune, F.A.C.P., New Canaan, Conn.
Dr. Kenneth Appel, F.A.C.P., Philadelphia
Dr. Fritz Talbot, F.A.C.P., Boston
Dr. Horace K. Richardson, F.A.C.P., Stockbridge
Dr. Robert B. Hiden (Associate), Stockbridge

The Twelfth Annual Meeting of the Florida East Coast Medical Association was held on November 10-11, 1939, at Ponte Vedra, Fla. The following members of the College took an active part in the program:

Dr. Clayton E. Royce, F.A.C.P., Jacksonville
Dr. Louie M. Limbaugh, F.A.C.P., Jacksonville

The following members of the College are Officers of the Association:

Dr. Edwin C. Swift, F.A.C.P., Jacksonville—Chairman, Program Committee
Dr. M. Jay Flipse, F.A.C.P., Miami—Vice President
Dr. Arthur J. Logie (Associate), Jacksonville—Secretary

On September 18, 1939, Dr. Philip J. Lukens (Associate), Ambler, Pa., was appointed Consulting Internist to the Norristown (Pa.) State Hospital.

Dr. Samuel A. Levinson, F.A.C.P., Chicago, delivered the Presidential Address on "History and Progress of the Scientific Work of the Cook County Coroner's Office" before the meeting of the Chicago Pathologic Society on October 9.

Dr. Walter C. Alvarez, F.A.C.P., Rochester, Minn., and Dr. Charles K. Maytum, F.A.C.P., Rochester, Minn., addressed the Chicago Society of Allergy on October 16 on "Gastro-Intestinal Allergy" and "Oxygen Therapy and X-Ray Therapy in Asthma," respectively.

Among lecturers appearing on the program of the New England Postgraduate Assembly, sponsored by the state medical societies of Massachusetts, New Hampshire, Rhode Island, Maine and Vermont, held at the Sanders Theater of the Harvard University, Cambridge, October 31–November 1, were:

Dr. James S. McLester, F.A.C.P., Birmingham, Ala.

"The Role of the Vitamins and Other Essential Substances in Human Nutrition"

Dr. Maurice C. Pincoffs, F.A.C.P., Baltimore, Md.

"Clinical Varieties of Hypertension"

Dr. Burton R. Corbus, F.A.C.P., Grand Rapids, Mich., was elected President of the Michigan State Medical Society at its recent annual session.

Dr. Henry I. Klopp, F.A.C.P., Allentown, Pa., has been elected President-Elect of the Pennsylvania Psychiatric Society, which was organized on October 5 at a meeting in Pittsburgh.

Dr. William C. Sandy, Director of the State Bureau of Mental Health, Harrisburg, was elected President, and announced "that the new society should exercise a statewide general leadership in psychiatry, being a coördinating body to which controversial and other questions of psychiatric interest may be referred for an authoritative opinion, should encourage general medical interest by participation in society meetings and should assist in developing and supporting proper psychiatric standards."

Under the Presidency of Dr. Willard C. Rappleye, F.A.C.P., New York City, the 50th annual meeting of the Association of American Medical Colleges was held at Cincinnati, October 23–25. Among the speakers was Dr. Walter Bauer, F.A.C.P., Boston, who spoke on "The Tutorial System in the Harvard Medical School."

The following members of the College were guest speakers at the one hundred and first semi-annual convention of the Southern California Medical Association, held at Santa Barbara, November 3–4:

Dr. W. Edward Chamberlain, F.A.C.P., Philadelphia—"Pitfalls in X-Ray Diagnosis"

Dr. Frank J. Heck, F.A.C.P., Rochester, Minn.—"Treatment of Pernicious Anemia and the Iron Deficiency Anemias."

Dr. Maurice P. Foley (Associate), Los Angeles, also addressed the meeting on "Present Day Concepts in the Treatment of Liver Disease."

Dr. Walter F. Donaldson, F.A.C.P., Pittsburgh, was reelected Secretary of the Medical Society of the State of Pennsylvania at its recent meeting in Pittsburgh. The 1940 Session of the above society will be held in Philadelphia.

Dr. Howard F. Root, F.A.C.P., Boston, delivered the Renziehausen Memorial Lecture on "Complications of Diabetes Mellitus," November 13 at the Mellon Institute, Pittsburgh.

Dr. Raymond L. Gregory, F.A.C.P., has been appointed Professor and Head of the Department of Medicine of the University of Arkansas School of Medicine, Little Rock.

The following Fellows of the College participated as guest speakers in a conference on convalescent care, sponsored by the New York Academy of Medicine, November 9-10:

Dr. O. H. Perry Pepper, F.A.C.P., Philadelphia
 Dr. William S. McCann, F.A.C.P., Rochester, N. Y.
 Dr. Lewellys F. Barker, F.A.C.P., Baltimore
 Dr. I. Ogden Woodruff, F.A.C.P., New York City

The program included the following subjects: physiology and psychology of convalescence, relation of chronic disease to convalescence, results of recent research in nutrition with particular reference to the convalescent state, institutional care for various types of patients, psychosomatic factors of convalescence and the socio-economic aspects of convalescent care.

Dr. Mary Hoskins Easby, F.A.C.P., Philadelphia, conducted a cardiac clinic at the scientific meeting held on December 1 in celebration of the 10th anniversary of the merger of the Woman's Hospital of Philadelphia and the West Philadelphia Hospital for Women, for all who have served as interns and residents at either institution.

During the seventieth annual session of the Medical Society of Virginia in Richmond, October 3-5, Dr. Walter B. Martin, F.A.C.P., Norfolk, was elected President-Elect of that society.

Among the speakers on the program of the 25th anniversary postgraduate conference of the Southwestern Medical Association, held at El Paso, Tex., November 9-11, were:

Dr. Samuel D. Ingham, F.A.C.P., Los Angeles—neurology
 Dr. Henry M. Winans, F.A.C.P., Dallas—medicine

Dr. Waller S. Leathers, F.A.C.P., Nashville, Tenn., was recently appointed President-Elect of the American Public Health Association.

The sixth annual cardiovascular institute, held under the auspices of the Heart Council of Greater Cincinnati, the West Virginia Heart Association and the Academy of Medicine of Cincinnati, was held at Cincinnati, Ohio, November 14, with the following Fellows of the College appearing on the program:

Dr. William M. Sheppe, F.A.C.P., Wheeling, W. Va.—"Syphilis of the Heart and Aorta"
 Dr. Oscar B. Biern, F.A.C.P., Huntington, W. Va., and Dr. Johnson McGuire, F.A.C.P., Cincinnati, Ohio—Round Table discussions on "Cardiovascular Syphilis"

Dr. Joseph I. Linde, F.A.C.P., New Haven, Conn., has been appointed a member of the Connecticut State Tuberculosis Commission, succeeding the late Dr. Stephen J. Maher.

Participating in the Postgraduate Extension Courses as instructors, now under way in the first, second, third, fourth and tenth districts of the State of Iowa, are the following Fellows of the College:

Dr. Fred M. Smith, Iowa City—"Diagnosis and Treatment of Coronary Thrombosis"

Dr. John H. Peck, Oakdale, Iowa—"Pulmonary Tuberculosis"

Dr. Daniel L. Sexton, St. Louis, Mo.—"Endocrine Therapy: Its Application in General Practice"

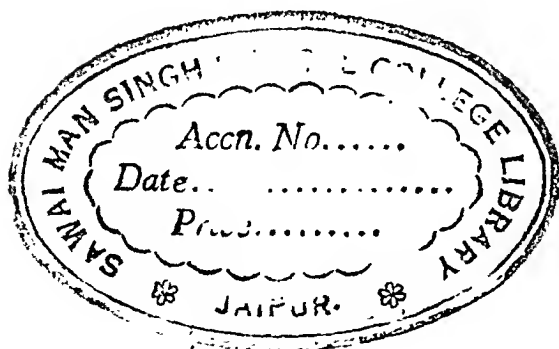
Dr. Lester R. Dragstedt, Chicago—"Endocrinology"

Dr. Henry W. Woltman, Rochester, Minn.—"Neuritis"

Dr. Edwin B. Winnett, Des Moines—"Management of Diabetes"

Dr. Edgar V. Allen, Rochester, Minn.—"Hypertension"

Dr. Ernest Kelley, Omaha—"The More Common Neurologic Conditions."



OBITUARIES

DR. FRANK J. WEIGAND

Dr. Frank J. Weigand, F.A.C.P., 60, of Richmond Hill, N. Y., and his wife, 61, were killed Sunday morning, October 29, 1939, when the doctor, it is believed lost control of his automobile.

Dr. Weigand was a native of Natick, Massachusetts, and had practiced in Richmond Hill since his graduation from Long Island Medical College, Brooklyn, in 1900. He had post-graduate training at the New York Lying-In Hospital, New York Skin and Cancer Hospital; he had been an Assistant in Obstetrics, Outpatient Department, Long Island College Hospital, 1900; Intern, Matteawan State Hospital, 1900-02; Junior Assistant Physician, Matteawan State Hospital, 1902-04; Assistant Physician, Dannemora State Hospital, 1905; Appointed Visiting Physician, Jamaica Hospital, 1919; Associate Physician, Jamaica Hospital, 1911-19; at the time of his death he was Visiting Physician and Member of the Educational Committee of the Medical Board, Jamaica Hospital; member of Dutchess County Medical Society, Queens-Nassau (County) Medical Society, Medical Society of the State of New York, the Brooklyn Neurologic Society, Brooklyn Pediatric Society, Greater New York Medical Society, Associated Physicians of Long Island, American Medical Association, and had been a Fellow of the American College of Physicians since 1931.

For years Dr. Weigand had been active in Boy Scout work and was the recipient of the Silver Beaver award, presented by the National Council for distinguished service to boyhood. At the time of his death he was a member of the camp committee and the health committee. He was active in Masonic circles, being a past master of Richmond Hill Lodge; a member of Ridgewood Chapter of the Royal Arch Masons, a past commander of Pilgrim Commandery of the Knights Templar and a member of Aurora Grata Consistory.

CHARLES F. TENNEY, M.D., F.A.C.P.,
Governor for Eastern New York

DR. MILTON ARLANDEN BRIDGES

Dr. Milton Arlanden Bridges, F.A.C.P., was born in New York City in 1894 and died on August 19, 1939. He received a B.S. degree from Columbia University and graduated from the Columbia University College of Physicians and Surgeons in 1919. He interned at the New York Post-Graduate Medical School and Hospital, 1918-20; was Resident Physician at New York Post-Graduate School and Hospital, 1920-22; Attending Physician, Hospital for Ruptured and Crippled, 1922-24; Consulting Physician to Sing Sing Hospital from 1924 for several years; Assistant Clinical Professor of Medicine, New York Post-Graduate Medical School, Columbia University;

Associate Attending Physician, Attending Physician to Outpatient Department and Chief of Diagnostic Clinic, New York Post-Graduate Medical School and Hospital; Director of Medicine and Attending Physician, Riker's Island Hospital; Consultant, Sea View Hospital (Staten Island); Diplomate of the American Board of Internal Medicine and Fellow of the American College of Physicians since 1926.

Dr. Bridges was extremely active in Masonry. He held many offices culminating in that of Master of Kane Lodge, F. and A. M., in 1938.

He belonged to the Sons of the Revolution, the Society of Colonial Wars, the Union League Club and Zeta Psi Fraternity.

Dr. Bridges was assistant medical director of the United States Olympic team (Paris) in 1924. He was an expert swimmer, having taught swimming and won countless medals during his college days. Swimming remained throughout his life the chief recreation of summer days.

From his fourteenth year on he was actively interested in magic, in his earlier years as an amateur performer and later as a collector of books, magazines, manuscripts, hand-bills, and other memoranda pertaining to magic and magicians. He carried on a heavy correspondence with magicians the world over. Many of these men who never met the doctor have been so touched by his death that they have taken the trouble to write to his widow expressing their heartfelt sorrow. Although magicians rated Dr. Bridges as an expert in sleight-of-hand technic, he was recognized as a great scholar and authority in the field of magic. His library, insured for twenty-five thousand dollars, contains over 5000 items. It is the largest American collection on the subject. It is noteworthy for the great number of autographed books. His collection of magical periodicals was very complete and he had a comprehensive knowledge of all the magazines and periodicals published on the subject. For several years he conducted a column in *The Sphinx*, in collaboration with John Mulholland, designated as "Magic Periodical History." Later he became review editor for this Journal. During the past decade Dr. Bridges rarely performed any magic; about five years ago he relinquished his membership in the Society of American Magicians because of the pressure of professional work, particularly his writings on the subject of nutrition. He did, however, keep abreast of every event in the world of magic and frequently entertained magicians as they passed through the metropolis. Innumerable magicians were given not only free medical advice but financial assistance as well.

Dr. Bridges was treasurer of the New York Medico-Surgical Society and a trustee of the New York Physicians Mutual Aid Association. In addition to his two books, "Dietetics for the Clinician" and "Food and Beverage Analyses," he made many contributions to the current literature. (About 20 papers of note since 1925.)

CHARLES F. TENNEY, M.D., F.A.C.P.,
Governor for Eastern New York

DR. MAURICE ISAAC STEIN

It is with deep regret that we note the death of Dr. Maurice Isaac Stein of Harrisburg, Pennsylvania, who died on August 15, 1939.

Dr. Stein was born in Baltimore, Maryland, on July 18, 1887. He received his degree of Doctor of Medicine from the University of Maryland School of Medicine in 1909. Dr. Stein took his postgraduate training at the Johns Hopkins Hospital, Mayo Clinic and Mt. Sinai Hospital in New York City.

Dr. Stein then became Visiting Gastro-Enterologist and Chief of Gastro-Intestinal Clinic at the Harrisburg Hospital.

His society affiliations were as follows: member of the Dauphin County Medical Society, the Pennsylvania State Medical Society, and the American Medical Association. Dr. Stein was a member and ex-President of the Harrisburg Academy of Medicine. He was elected an Associate of the American College of Physicians on April 3, 1938.

EDWARD L. BORTZ, M.D., F.A.C.P.,
Governor for Eastern Pennsylvania

DR. HERMAN BRYDEN ALLYN

Dr. Herman Bryden Allyn, aged 79, died at his home, 20 South 39th Street, Philadelphia, on November 6, 1939.

Dr. Allyn was graduated from the University of Pennsylvania School of Medicine in 1885 and took his postgraduate education at the Philadelphia Polyclinic Hospital and in Leipzig, Germany. He obtained his license to practice in 1886.

Dr. Allyn became Clinical Professor of Medicine at the Woman's Medical College of Pennsylvania, Associate in Medicine at the University of Pennsylvania School of Medicine, and Visiting Physician to the St. Joseph's Hospital.

During the World War, Dr. Allyn was Contract Surgeon from 1917 to 1918 and Chief of Medical Service caring for the personnel of the American Red Cross in Paris, 1918-19.

Dr. Allyn was elected a member of The Philadelphia County Medical Society in 1888 and became the 59th President of the Society serving during the year 1920. Other society affiliations included membership in the College of Physicians, Pathological Society of Philadelphia, Pediatric Society of Philadelphia, American Medical Association, the American Heart Association, and the Medical Society of the State of Pennsylvania; he had been a Fellow of the American College of Physicians since January 30, 1920.

It is with the deepest regret that we note the passing of this outstanding Philadelphia physician.

EDWARD L. BORTZ, M.D.,
Governor for Eastern Pennsylvania

DR. ALBERT BERNARD YUDELSON

Dr. Albert Bernard Yudelson (Associate), Chicago, Ill., died of a coronary thrombosis August 27, 1939. He had sustained prior attacks of this kind and had not been in practice for some years.

Dr. Yudelson was born in 1872 and graduated from Northwestern University Medical School in 1906. Later he was for some time Associate Professor of nervous and mental diseases in his alma mater. For many years he was attending neurologist at the Wesley Memorial Hospital. He was a member of the Chicago Medical Society, the Illinois State Medical Society and the American Medical Association, the Chicago Pathological Society, the Central Neuropsychiatric Association and the Association for the Study of Internal Secretions. He served a term as President of the Chicago Neurological Society. He has been an Associate of the American College of Physicians since 1925.

It was my privilege to have known Dr. Yudelson quite well and I gladly express my appreciation of his fine character and many splendid traits. He was a loyal friend, a man of the highest integrity, devoted to his family, conscious of his obligations to his patients, a hard working physician, a constant student, and an excellent neurologist.

For some years he had been incapacitated, but I am sure that I speak for the men who have known him well and were associated with him through many years in teaching and practice. Dr. Yudelson was an exceptionally high minded and attractive man.

JAMES G. CARR, M.D., F.A.C.P.,
Governor for Northern Illinois

